

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

IPR2023-00546
U.S. Patent No. 10,450,611

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,450,611**

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Ex. 1002	Rebecca J. Leary <i>et al.</i> , “Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing,” <i>Science Translational Medicine</i> (2010) (Leary)
Ex. 1003	Quake <i>et al.</i> , WO 2011/057061 (Quake)
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Ex. 1006	Florian Mertes <i>et al.</i> , “Targeted enrichment of genomic DNA regions for next-generation sequencing, Briefings in Functional Genomics,” <i>Briefings in Functional Genomics</i> (2011) (Mertes)
Ex. 1007	Lira Mamanova <i>et al.</i> , “Target-enrichment strategies for next-generation sequencing,” <i>Nature</i> (2010) (Mamanova)
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Ex. 1009	Unused
Ex. 1010	<i>Personalis v. Foresight</i> , First Amended Complaint, D. Colo., Case No. 1:22-v-01913, Dkt. 9, filed August, 17, 2022 (“FAC”)
Ex. 1011	Unused
Ex. 1012	Timothy J. Ley <i>et al.</i> , “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” <i>Nature</i> (2008) (Ley)
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Ex. 1014	Jeffrey S. Ross and Maureen Cronin, “Whole Cancer Genome Sequencing by Next-Generation Methods,” <i>American Journal of Clinical Pathology</i> (2011) (Ross)

Ex. 1015	David J. McBride, et al., “Use of Cancer-Specific Genomic Rearrangements to Quantify Disease Burden in Plasma from Patients with Solid Tumors,” <i>Genes, Chromosomes & Cancer</i> (2010) (McBride)
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Ex. 1041	H. Li, "Mapping short DNA sequencing reads and calling variants using mapping quality scores," Genome Res. (2008) (<i>Li</i>)
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Ex. 1074	S. Misawa, et al., “Significance of chromosomal alterations and mutations of the N-RAS and TP53 genes in relation to leukemogenesis of acute myeloid leukemia,” <i>Leukemia Research</i> (1998) (Misawa)
Ex. 1075	S. Davies, et al., “Indications for Hematopoietic Cell Transplantation in Acute Leukemia,” <i>Biology of Blood and Marrow Transplantation</i> (2008) (Davies)
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I. INTRODUCTION

Foresight Diagnostics Inc. (“Petitioner”) requests *inter partes* review and cancellation of claims 1-5, 9-11, 13, 18, 19, and 28-30 of U.S. Patent No. 10,450,611 (“the ’611 patent”), entitled “Personalized Genetic Testing.”

For the reasons set forth below, and as further explained in the declaration of Petitioner’s expert genome scientist John Quackenbush, Ph.D., Ex. 1061 (“Quackenbush”), the challenged claims should be cancelled.

II. GROUNDS FOR STANDING

Petitioner certifies that the ’611 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging its claims on the grounds identified in this petition.

III. MANDATORY NOTICES

A. Real Party-In-Interest

Petitioner Foresight Diagnostics Inc. is the real party-in-interest with respect to this petition for *inter partes* review.

B. Related Matters

On August 2, 2022, Patent Owner filed a lawsuit against Petitioner alleging infringement of the ’611 patent and other patents assigned to Patent Owner. The case is pending in the United States District Court for the District of Colorado, bearing case number 1:22-cv-01913. Ex. 1010 (First Amended Complaint).

IPR2023-00546

U.S. Patent No. 10,450,611

The '611 patent issued from Application No. 15/793,845, which claims priority to provisional Application No. 62/342,674 and PCT/US2017/034823.

C. Lead and Back-up Counsel and Service Information

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IV. THE '611 PATENT

According to its face, the '611 patent issued on October 22, 2019 from Application No. 15/793,845. Ex. 1001, codes (45), (21). The '611 patent claims priority to Provisional Application No. 62/342,674, filed on May 27, 2016. *Id.*, code (60). According to Patent Center, the '845 Application was asserted to fall under the AIA's first inventor to file provisions:

Application #	Attorney Docket #	Patent #	Status	Filing or 371 (c) date
15/793,845	44168-711.301	10,450,611	Patented Case - 10/02/2019 Issued - 10/22/2019	10/25/2017
Application type	Utility	Earliest publication #	US 2018-0051338 A1	Intl. registration # (Hague)
Examiner	-	Earliest publication date	02/22/2018	Intl. registration publication date
Group art unit	1634	Assignee for publication	-	-
Class/subclass	435/006.100	Confirmation #	2020	
AIA (first inventor to file)	Yes			
Entity status	Small			

The '611 patent purports to disclose “methods and systems for personalized genetic testing of a subject,” which performing “a sequencing assay . . . on a biological sample from the subject, which then leads to genetic information related to the subject. Next, nucleic acid molecules are array-synthesized or selected based on the genetic information derived from data of the sequencing assay. At least some of the nucleic acid molecules may then be used in an assay which may provide additional information on one or more biological samples from the subject or a

biological relative of the subject.” Ex. 1001, Abstract. The patent conclusorily states that the “methods disclosed herein may comprise providing a therapeutic intervention, such as, for example, treating and/or preventing a disease or condition in a subject based on one or more biomedical outputs. The one or more biomedical outputs may recommend one or more therapies.” *Id.* at 55:65-56:2. However, the specification provides no data or working examples of any clinical application of the alleged invention, let alone any data or working example supporting the claims as issued.

V. LEVEL OF ORDINARY SKILL IN THE ART

As Dr. Quackenbush explains, a POSA in the field of the '611 patent:

[W]ould have had an advanced degree (such as an M.D. or the equivalent of a Ph.D. in a life or physical sciences, engineering, or mathematics discipline), and through further education or postdoctoral experience, an understanding of various sequencing and next generation sequencing methods, sample preparation methods, targeted enrichment methods, bioinformatics methods for interpreting sequencing data, and methods for identifying genetic variants in a sample. A POSA also would have had an understanding of clinical applications of sequencing technology to conditions associated with nucleic acid variation, such as cancer, non-invasive prenatal testing, and transplant rejection. Additionally, a POSA would have had an understanding of cancer biology as it relates to mutations associated with tumor diagnosis, progression, and treatment, as well as awareness

of the various types of mutations that can occur in and influence the course of a patient's cancer.

Quackenbush ¶37.

VI. BACKGROUND KNOWLEDGE OF A POSA

A. Genes and Mutations

Genes contain the set of instructions for the development and maintenance of the cells of all organisms. Genes are made of deoxyribonucleic acid (“DNA”) and are located on chromosomes. Certain alterations, sometimes called “mutations,” “variations,” “variants,” or “polymorphisms,” can occur in all genes and portions of the human genome, contributing both to normal patterns of human variation as well as individual risk for developing diseases. Polymorphisms can include many types of genomic alteration, including insertions, deletions, point mutations, translocations, rearrangements, and copy number variations. The entire collection of an individual's genetic variants is referred to as their “genotype.” *Id.* ¶¶39-52.

Genetic mutations can be inherited (i.e., passed on from their parents to their offspring) or acquired (i.e., developed for the first time in a new cell). Inherited mutations are called “germline” mutations. Acquired, or non-inherited, mutations are called “somatic” mutations. Somatic mutations unique to a particular tumor can be a useful tool for detecting, tracking, and monitoring a patient's cancer. *Id.* ¶53.

Mutations known in the art included single nucleotide polymorphisms (“SNPs”), copy number variants (“CNVs”), and insertions or deletions (“indels”).

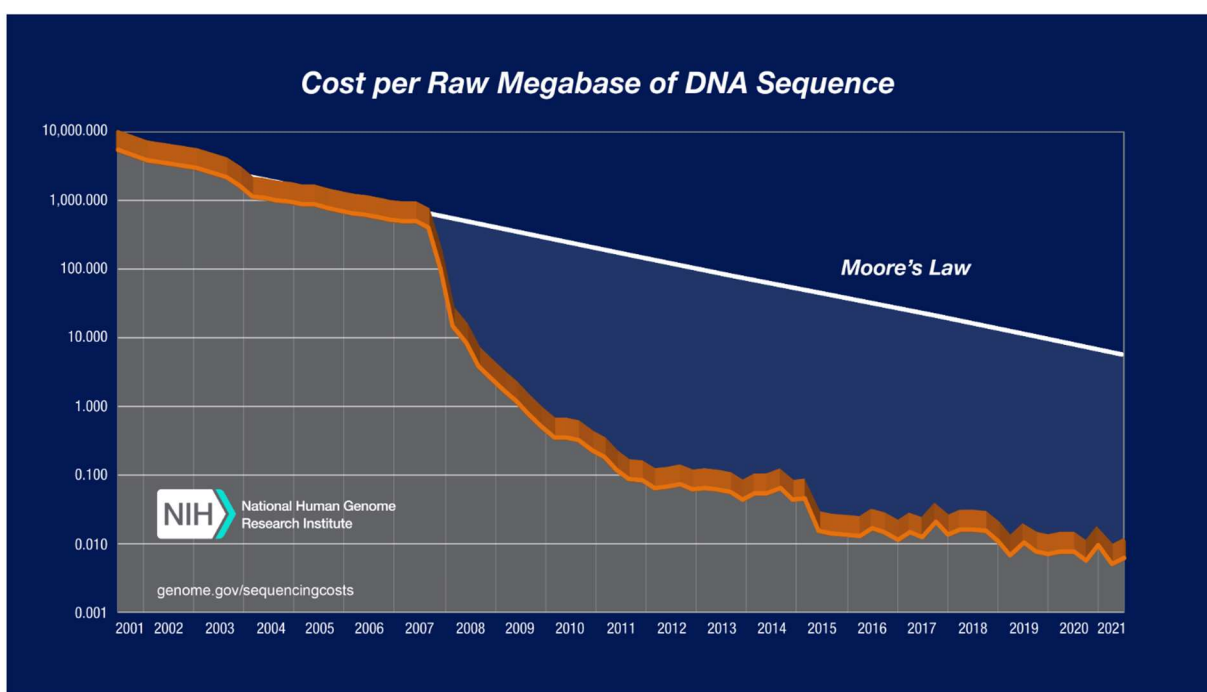
An SNP (sometimes called a single nucleotide variant (“SNV”)) is a change in one DNA base pair that may result in the substitution of one amino acid for another in the protein that is encoded by the gene. A POSA would have also been familiar with translocations, which involve the relocation of a gene from one chromosomal location to another. By 2013, many publicly accessible databases existed in which a POSA would have been able to search for a large number of catalogued cancer-associated mutations. *Id.* ¶¶54-56.

B. Nucleic Acid Sequencing

A POSA would have been familiar with multiple techniques for nucleic acid “sequencing,” i.e., determining the order of the bases in a nucleic acid molecule at the base-by-base level. For many years, sequencing was performed using “Sanger” sequencing, which terminates the synthesis of a template strand of DNA at different lengths. These different length DNA strands can be “read” to derive the DNA sequence. *Id.* ¶¶57-61.

By around 2005, a new approach to sequencing called “next generation sequencing” (“NGS”), sometimes also called “massively parallel sequencing” or “sequencing by synthesis,” had been developed to allow multiplex sequencing of many different sequences simultaneously. By approximately 2008, techniques for NGS were well-known and commercially available. *See, e.g.,* Ex. 1013. NGS is a high-throughput method for determining the base-by-base sequences of nucleic acid

molecules, such as DNA. NGS is exponentially faster, cheaper, and more efficient than Sanger sequencing, though both techniques provide accurate sequence information. Quackenbush ¶¶62-64. See also Ex. 1019 (<https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data>).



Sequencing cost per megabase - 2021

C. Sequencing Depth and Read Counts

NGS has been applied widely to sequencing of genomic sequences. It was known well before May 2016 that different applications would involve different levels of sequencing, or sequencing depths. Generally, to obtain highly accurate sequencing information, it is necessary to sequence accessible parts of the target genomic sequences multiple times. Reasons for this include (i) multiple observations

per base are required to have confidence that the base “call” is correct, so that errors that might occur in any one sequencing read can be rejected; (ii) so that mutation calls can be made with confidence based on multiple independent sequencing reads exhibiting the same polymorphism; and (iii) since DNA is randomly fragmented before sequencing and the amplification and library construction process may introduce some biases, sequencing reads are not evenly distributed throughout the genome, meaning that some bases will be read more than other bases. Ex. 1028 (Illumina Technical Note, “Estimating Sequencing Coverage”); Quackenbush ¶65.

“Coverage,” “sequencing depth,” or “depth of sequencing” are terms that refer to the number of times genomic sequence has been sequenced. It can be calculated by the formula:

$$C=L*(N/G)$$

Where C stands for coverage, G is the haploid genome length (~3 billion basepairs for the human genome), L is the read length, and N is the number of reads. Quackenbush ¶66. By 2010, whole-genome sequencing to 30x coverage was routine on the commercially available Illumina HiSeq 2000. Ex. 1028 (Illumina Specification Sheet, 2010) (“With unmatched cost-effectiveness, HiSeq 2000 is the first commercially available sequencer to enable researchers to obtain ~30x coverage of two human genomes in a single run for under \$10,000 USD per sample.”; “The ultra-high output and speed of HiSeq 2000 now make it possible to sequence two

human genomes at ~30x coverage simultaneously . . .”). One run of the HiSeq 2000 allowed for a billion single-end reads or two billion paired-end reads (sequencing reads from both ends of a DNA fragment). *Id.* at 2. As each read was 100 bases in length, for 2 billion reads, the formula above yields 66.67x coverage for a single genome or 33.33x coverage of two genomes. Quackenbush ¶66.

Whole genome sequencing experiments that sought to ensure more complete coverage of the genome could do so by sequencing to greater depth. For example, in 2012, Lam reported performing whole genome sequencing to an average coverage of ~76x using the HiSeq2000 and a different sequencing platform from Complete Genomics. Ex. 1029 at 78. Sequencing to even greater depth was also routine, as it only required additional runs of the sequencer: “it is very easy to increase the coverage or sequence depth, if you later decide you need more data. Provided you still have your original sample, you can just sequence more, and combine the sequencing output from different flow cells.” Ex. 1028 at 2; Quackenbush ¶67.

In February 2014, Sims reviewed many published sequencing studies. Ex. 1040. In particular, Sims reviewed all the sequences from the Illumina platform deposited from 2012 to June 2013 by 771 different studies into the European Nucleotide Archive (<https://www.ebi.ac.uk/ena>). Sims found that the number of bases sequenced per sample for whole genome sequencing and whole exome sequencing varied widely. For whole genome sequencing, the range was about 0.1

GB to over 200 GB. *Id.* at 123, Figure 1. For whole exome sequencing, the range was about 0.2 GB to 20 GB. *Id.* Indeed, scientists chose the number of bases sequenced based on the goal of the particular sequencing project.

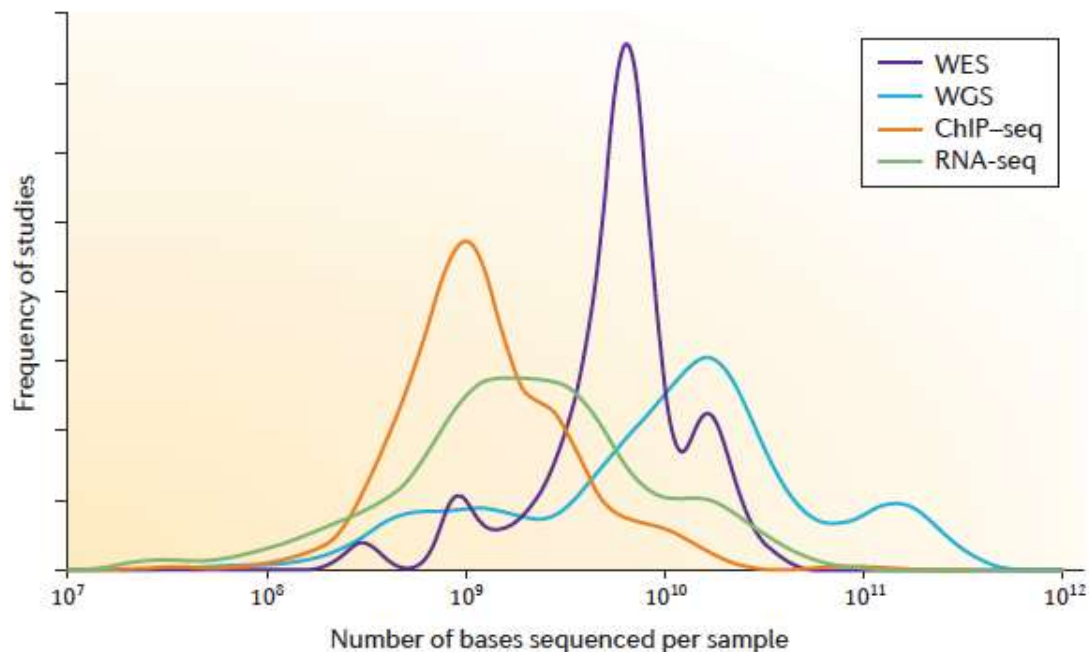


Figure 1 | Sequencing depths for different applications. The frequency of studies that use read counts of all runs (which are typically flow-cell lanes) and that were deposited from 2012 to June 2013 for the Illumina platform in the European Nucleotide Archive (ENA) is shown. The plot provides an overview of sequencing depths that are usually chosen for the four most common experimental strategies. Densities have been smoothed and normalized to provide an area under the curve that is equal to one. The depth and therefore the cost of an experiment increase in the order of chromatin immunoprecipitation followed by sequencing (ChIP-seq), RNA sequencing (RNA-seq), whole-exome sequencing (WES) to whole-genome sequencing (WGS). Although ChIP-seq, WES and WGS have typical applications and thus standardized read depths, the sequencing depth of RNA-seq data sets varies over several orders of magnitude. Multimodal distributions of WES and WGS reflect different target coverage. To generate this figure, runs were summed by experiment and, for each study, one experiment was chosen at random to avoid counting large studies more than once. Note that the ENA archive only contains published data sets and excludes medically relevant data sets. The plot was created from 771 studies.

D. Amplification and Enrichment

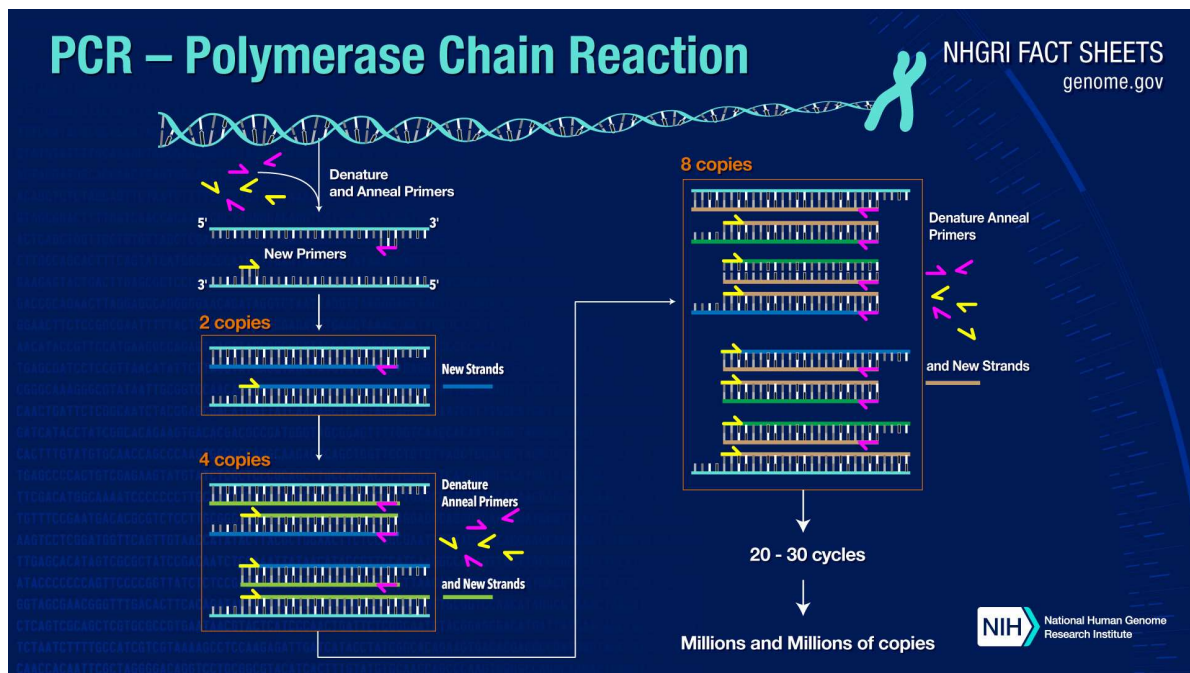
Both Sanger sequencing and NGS require sufficient quantities and/or relative abundances of target DNA. Thus, well before 2016, several techniques had been developed to generate or isolate copies of DNA molecules of interest to facilitate sequencing, including enrichment of desired targets on solid substrates like DNA microarrays. A POSA would have been familiar with a number of such techniques, including PCR and solution-phase hybridization. *Id.* ¶¶69-72. Each technique has certain benefits over the others, but in many applications they were used relatively interchangeably by those skilled in the art. *Id.* ¶72. *See* Ex. 1006 (Table 1) (describing pros, cons, and overlapping applications of “[c]urrently employed targeted enrichment techniques” as of 2011).

Table 1: Currently employed targeted enrichment techniques

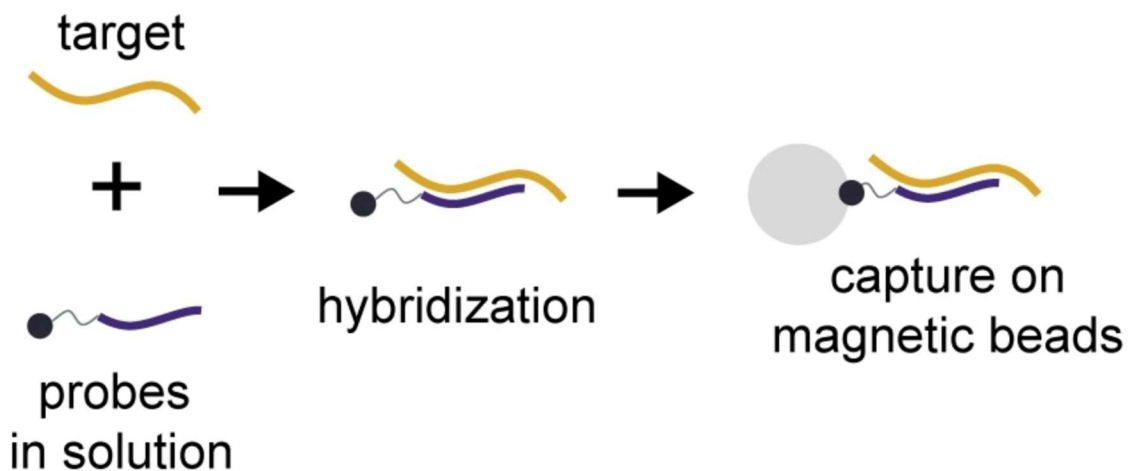
Enrichment technique	Vendor	Features	Pros	Cons	Number of loci (target size)	Library prep for NGS
Hybrid capture						
Solid support	Agilent SureSelect, Roche NimbleGen SeqCap EZ	Medium to large target regions, custom and pre-configured target regions	Ease of production, large target sets	Large amount of input DNA, high-tech equipment (3–10 µg)	10^4 – 10^6 (1–50 Mb)	Before enrichment
In solution	Agilent SureSelect, FlexGen ReSelect, MTCarray MSelect, Roche NimbleGen SeqCap EZ	Regions (i.e. whole exome), Multiplexing possible, ready to use kits	Ease of use, small amount of input DNA (<1–3 µg)			
Circularization						
Molecular inversion probes	HaloGenomics	Custom kits and clinically relevant panel kits	No dedicated instruments, high specificity, input DNA (<1 µg)	exome kit not available yet	10^2 – 10^4 (0.1–5 Mb) 10–200 (0.1–1.5 Mb)	During enrichment (incorporated into hybridization probes)
Selector probes						
PCR						
Long range	Invitrogen, SequelPrep, Qiagen SeqTarget system	Smaller target regions, coverage by tiling	Relatively easy to set up and automatable, even coverage	PCR conditions largely influence effectiveness, >10 µg DNA for Large sets	10^2 – 10^4 (0.1–5 Mb)	After enrichment
Multiplex	Multiplexcom, Fluidigm	Smaller target regions, coverage by tiling, multiplex PCR of 150–200 amplicons (150–450 bp)	Easy to perform, reasonably economical in terms of, even coverage			
Micro droplet	RainDance	Smaller target regions, coverage by tiling, micro droplet PCR of up to 20 000 amplicons (150–1500 bp)	Even coverage, low input DNA	Relatively expensive, specialist equipment	10^2 – 10^4 (up to 10 Mb)	

All major targeted enrichment techniques show relative pros and cons.

In PCR, DNA molecules are replicated in a manner that leverages the base pairing of complementary DNA strands. In PCR, strands of double-stranded DNA are first completely separated, leaving two complementary single-stranded DNA strands, which serve as templates for replication. PCR “primers” or “probes,” which are short oligonucleotides that are complementary to a small portion of the DNA templates, can then be created. These primers/probes then hybridize (i.e., bind through base pairing interactions) to, and thus “capture,” the target region of interest on the DNA template strand. After the PCR primer hybridizes to that target sequence, an enzyme called a “polymerase” synthesizes a new nucleic acid molecule complementary to the single-stranded DNA template. This process can be repeated, resulting in the exponential amplification of the target sequence. *Id.* ¶¶73-78.



A POSA would also have been familiar with the use of solution-based hybridization techniques for target enrichment. In short, this technique works by mixing in solution the target DNA with an abundance of short nucleic acid “baits.” Like the primers in the PCR approach, these “baits” hybridize to the target DNA sequence of interest. The baits may also include an additional component, such as biotin, that binds to a magnetic bead following the hybridization step.



When such beads are mixed into the solution, the target sequence is captured through bead-probe binding, and the target DNA can be isolated by washing away the non-target, and hence unbound, DNA and then removing the beads and baits. These techniques were well-characterized and widely used well before the priority date, and a number of commercial vendors offered off the rack and on-demand solutions to implement this approach. *Id.* ¶¶79-81. *See also* Ex. 1005, Ex. 1006.

E. Personalized Biomedical Monitoring

Once “[w]hole-genome sequencing [became] possible at reasonable cost and timeframe,” *Ley* “use[d] this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes.” *Id.* *Ley* established that a useful approach to cancer monitoring is to first fully characterize the patient’s tumor using whole-genome sequencing to identify polymorphisms of interest, and then serially monitor those polymorphisms to track the tumor over time. As Dr. Quackenbush explains, a POSA would have appreciated that in *Ley*’s approach, the results of the initial whole-genome sequencing step would help clinicians avoid “miss[ing] key mutations,” and allow them to create a specific set of probes to capture regions of interest harboring the identified mutations for further sequencing. Quackenbush ¶¶82-85. Shortly thereafter, *Leary* and *McBride* demonstrated the successful use of the same concept, using structural variants (as opposed to SNPs/SNVs in *Ley*) to serially monitor tumor DNA in the blood plasma of patients presenting with solid tumors. *Id.* ¶86. Those skilled in the art further developed ways to report the information obtained via such clinical protocols, and ways to leverage that information, for example by identifying appropriate clinical trials or targeted therapies. *Id.* ¶¶91-94.

Moreover, the use of whole-genome sequencing to develop targeted monitoring assays was not limited to cancer, because the fundamental properties of nucleic acids that enable this mode of analysis are universal. For example, by 2009,

methods of analyzing nucleic acids to aid the diagnosis of transplant rejection had been developed. Ex. 1003. Those methods, similar to those applied in cancer surveillance, were based on the fact that a transplanted organ will have a different genetic fingerprint (a different genotype, coming from the organ donor) than the transplant recipient, and that once identified, that fingerprint may be used to detect transplant rejection by monitoring the levels of cell free DNA (cfDNA) observed in the transplant recipient's blood. The underlying science is that the cfDNA will be a mix of DNA from the recipient and the donor and that the unique variants in the donor's DNA will allow that DNA to be detected. *See generally id.* ¶¶40-50, 69-70. **Quake** observed that such methods were analytically similar to those used to detect and monitor cancer. *Id.* ¶41. Following whole-genome sequencing, **Quake** explained that serial PCR or NGS assays could be employed to “detect, identify, and/or quantify” the donor specific markers in the transplant recipient following transplantation. *See id.* ¶¶47-48, 73-75; Quackenbush ¶¶87-90.

VII. KEY PRIOR ART

A. Ley

Ley et al., “DNA sequencing of a cytogenetically normal acute myeloid leukemia genome,” is an article that was published in *Nature* by November 6, 2008. Ex. 1012; Quackenbush ¶95. **Ley** is therefore prior art to the '611 patent. *See* Section VI.D (summarizing findings of **Ley**).

B. Newman

Newman et al., “Integrated digital error suppression for improved detection of circulating tumor DNA,” is an article that was published in *Nature Biotechnology* by May 2016. Ex. 1043. It was published online on March 28, 2016. Ex. 1060 (Newman Declaration). *Newman* is therefore prior art to the ’611 Patent.

VIII. GROUNDS FOR THE CHALLENGES

Petitioner challenges the claims of the ’611 patent on the following grounds:

	Challenged Claims	Prior Art
1	1-2, 4-5, 9-11, 13, 18, 19, 28-30	Anticipated (35 U.S.C. § 102(a)) by <i>Ley</i> (Ex. 1012)
2	1-5, 9-11, 13, 18, 19, 28-30	Obvious (35 U.S.C. § 103(a)) over <i>Ley</i> (Ex. 1012)
3	1-5, 9-11, 13, 18, 19, 28-30	Anticipated (35 U.S.C. § 102(a)) by <i>Newman</i> (Ex. 1043)
4	1-5, 9-11, 13, 18, 19, 28-30	Obvious (35 U.S.C. § 103(a)) over <i>Newman</i> (Ex. 1043)

The references of the grounds were not previously considered by the Office during the prosecution of the ’611 patent.

IX. CLAIM CONSTRUCTION

“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir.

2011). Petitioner does not believe that any term requires express construction for purposes of this proceeding, and has applied the claims as a POSA would have understood them in view of Patent Owner's application of the claims to Petitioner's methods in the litigation, as explained for certain terms below.

While Petitioner and Dr. Quackenbush have identified claim 2, the claim containing the limitation requiring "outputting a report," in the prior art, this limitation is not entitled to patentable weight under the printed matter doctrine because it merely conveys information and is not functionally related to the substrate on which it is provided.

A. "probe"

The '611 patent explains that probes can be used in a hybridization array, by "synthesizing the plurality of nucleic acid probe molecules using at least one array" Ex. 1001 at 4:54-55; *see also id.* at 7:18-20 (probes include "synthesizing the plurality of nucleic acid probe molecules on a single solid substrate."). The '611 patent also explains that "nucleic acid probe molecules comprise primers for amplifying the nucleic acid sequences," *id.* at 5:16-18, and that "the plurality of nucleic acid probe molecules of the assay enrich or deplete a nucleic acid mixture of nucleic acid molecules for target regions, by hybridization or amplification." *Id.* at 6:64-67. As Dr. Quackenbush explains, based on this intrinsic record, a POSA would have understood that the claimed "nucleic acid probe molecules" include PCR

primers, hybrid capture baits, and other such nucleic acid probe molecules for selectively amplifying or enriching sequences. Quackenbush ¶98.

B. “report”

The '611 Patent explains that “[s]ome embodiments comprise outputting a report that is indicative of a presence or absence of the at least the subset of the genetic variants in the subject or the at least one biological relative.” Ex. 1001 at 5:13-16. Further, Figure 1 of the '611 Patent is consistent with the plain meaning of the term. It shows a therapeutic intervention, which can be a report, at the end of a process that includes personalized assays:

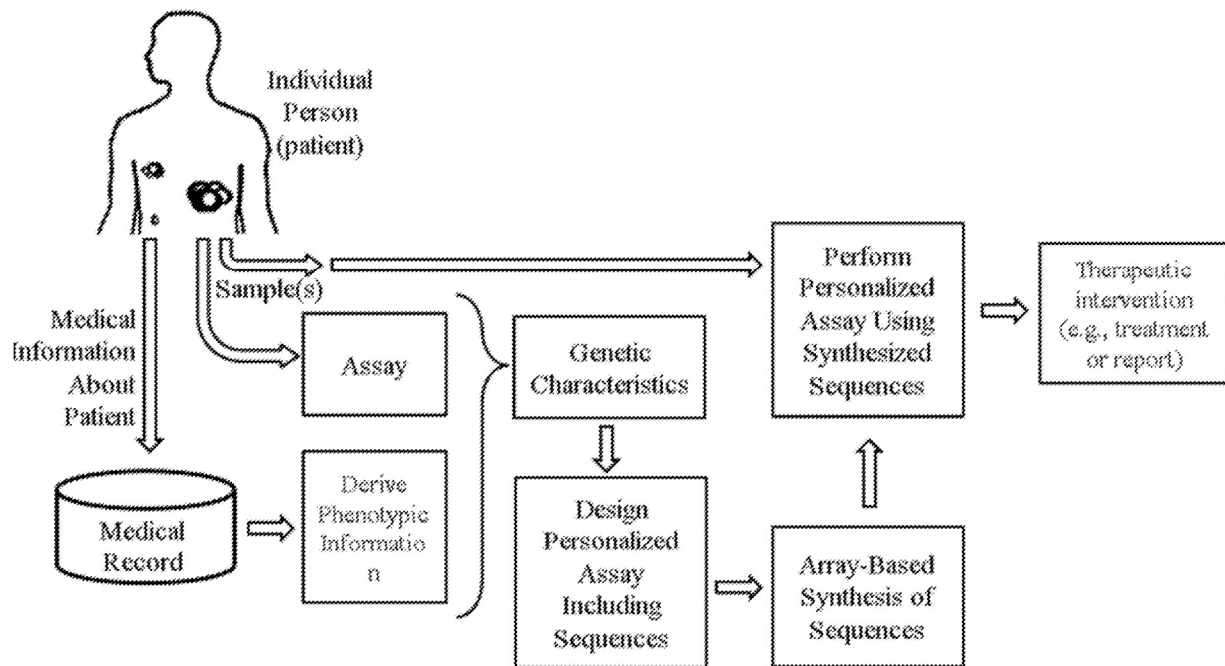


FIG. 1

As Dr. Quackenbush explains, based on this intrinsic record, a POSA would have understood that the claimed “report” includes, for example, providing information for treatment of a patient as well as providing an indication of genetic variation. Quackenbush ¶¶99-100.

X. LISTING OF CHALLENGED CLAIMS

1. A method for personalized genetic testing, comprising:
 - (a) sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more;
 - (b) computer processing said sequencing data to identify a plurality of nucleic acid sequences having a set of genetic variants, wherein said set of genetic variants are identified with respect to a reference;
 - (c) obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample;
 - (d) using said probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in an additional biological sample from said subject or at least one biological relative of said subject, to generate a sequencing library; and
 - (e) subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

2. The method of claim 1, further comprising outputting a report that is generated at least based on comparison of results from said sequencing of (a) with results from at least said subjecting said sequencing library to said sequencing of (e).

3. The method of claim 1, wherein in said sequencing of (a), said at least one biological sample is obtained from said subject at a first time point, and wherein said additional biological sample is obtained from said subject or said at least one biological relative at a second time point subsequent to said first time point.

4. The method of claim 1, wherein said sequencing of (a) comprises (i) exome sequencing, (ii) sequencing a panel of genes, (iii) whole genome sequencing, and/or (iv) sequencing a population of complementary deoxyribonucleic acid molecules derived from ribonucleic acid molecules.

5. The method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).

9. The method of claim 1, further comprising outputting a report that identifies said presence or absence of said at least said subset of said genetic variants in said subject or said at least one biological relative.

10. The method of claim 1, further comprising providing a therapeutic intervention at least based on said presence or absence of said at least said subset of said genetic variants identified in (e).

11. The method of claim 1, wherein said at least one biological sample includes a tumor sample and said nucleic acids molecules are from cells in said tumor sample.

13. The method of claim 1, wherein said plurality of nucleic acid sequences having said set of genetic variants comprises genetic variants in a germline sequence of said subject.

18. The method of claim 1, wherein subjecting said sequencing library to sequencing in (e) comprises generating nucleic acid sequence data from said additional biological sample.

19. The method of claim 1, wherein computer processing of said sequence data comprises identifying one or more of (i) genetic variants of said nucleic acid sequence with respect to a germline sequence(s), (ii) alleles which match said reference sequence(s) and are correlated with a type of cancer or other disease, (iii) alleles which determine a human leukocyte antigen (HLA) type, (iv) metrics of gene expression or allele-specific expression, and (v) quantification of non-coding ribonucleic acid (RNA) molecules or micro-RNA molecules which are at least partially tissue-type specific or cancer-type specific.

28. The method of claim 1, further comprising using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.

29. The method of claim 1, wherein said reference comprises a human reference sequence.

30. The method of claim 1, wherein said reference is a human reference sequence.

XI. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS**A. Ground 1: Ley Anticipates Claims 1, 2, 4, 5, 9-11, 13, 18, 19, 28-30**

As set forth below, and as explained by Dr. Quackenbush in paragraphs 101-159 of his declaration, claims 1, 2, 4, 5, 9-11, 13, 18, 19, and 28-30 are anticipated by *Ley*.

Ley discloses a method of genetic testing that used “massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient” with leukemia. Ex. 1012 (*Ley*) at 66. The genetic testing described in *Ley* was “personalized” given that the assay sequenced the patient’s tumor’s genome and compared “its matched normal counterpart obtained from the same patient’s skin.” *Id.*; Quackenbush ¶103. Through this personalized genetic testing, Ley “discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse. . . .” Ex. 1012 (*Ley*) at 66; Quackenbush ¶103.

1. Claim 1

Claim 1 recites “[a] method for personalized genetic testing” comprising method steps 1(a)-1(e). To the extent the preamble is limiting, *Ley* discloses it. The genetic testing described in Ley was “personalized” given that the assay sequenced the patient’s tumor’s genome and compared it to a reference sequence, but also

compared it to “its matched normal counterpart obtained from the same patient’s skin.” Ex. 1012 at 66; Quackenbush ¶104.

a) “sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more”

Ley discloses the use of whole genome sequencing to sequence nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more. Quackenbush ¶¶105-07. For example, *Ley* “used massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient with a typical presentation of French-American-British (FAB) subtype M1 acute myeloid leukaemia (AML) with normal cytogenetics.” Ex. 1012 at 66. Further, *Ley* discloses that the sequencing comprises sequencing 12 gigabases (GB) or more at least because *Ley* states that, for example, “[f]or the tumour genome, 32.7 ‘haploid’ coverage (98 billion bases) was obtained, and 13.9-fold coverage (41.8 billion bases) was obtained for the normal skin sample.” *Id.* Both figures—“98 billion bases,” or 98 GB, and “41.8 billion bases,” or 41.8 GB—are over the claimed 12 GB lower limit. Quackenbush ¶106.

b) “computer processing said sequencing ...”

Ley discloses computer processing the sequencing data to identify a plurality of nucleic acid sequences having a set of genetic sequences. Quackenbush ¶¶108-

14. For example, *Ley* explains that “[t]he analysed reads were aligned to the human reference genome (NCBI Build 36) using Maq.” Ex. 1012 at 71. As Dr. Quackenbush explains, a POSA would have known that Maq was one of many software tools (implemented on a computer) available at the time to perform alignments of sequence data to a reference genome (process sequence information) as this was a universal practice in the analysis of sequence data. Quackenbush ¶109.

Further, *Ley* states that the sequencing identified a large number of genetic variants with respect to a reference. *Id.* ¶110. *Ley* identifies genetic variants with respect to “human reference genome (NCBI Build 36).” Ex. 1012 at 71. Also, Table 1 from *Ley* describes numerous variants:

Table 1 | Tumour and skin genome coverage from patient 933124

	Tumour	Skin
Libraries	4	3
Runs	98	34
Reads obtained	5,858,992,064	2,122,836,148
Reads passing quality filter	3,025,923,365	1,228,177,690
Bases passing quality filter	98,184,511,523	41,783,794,834
Reads aligned by Maq	2,729,957,053	1,080,576,680
Reads unaligned by Maq	295,966,312	138,276,594
SNVs detected with respect to hg18 (no Y)	3,811,115	2,918,446
SNVs (chr 1–22) detected with respect to hg18	3,681,968 (100.0%)	2,830,292 (100.0%)
SNVs also present in dbSNP	2,368,458 (64.3%)	2,161,695 (76.4%)
SNVs also present in Venter genome	1,499,010 (40.7%)	1,383,431 (48.9%)
SNVs also present in Watson genome	1,573,435 (42.7%)	1,456,822 (51.5%)
SNVs not in dbSNP/Venter/Watson	1,223,830 (33.2%)	591,131 (20.9%)
SNVs not in dbSNP/Venter/Watson/skin	925,200 (25.1%)	—
HQ SNPs	46,494 (100.0%)	46,572 (100.0%)
HQ SNPs where reference allele is detected	42,419 (91.2%)	38,454 (82.6%)
HQ SNPs where variant allele is detected	43,164 (92.9%)	39,220 (84.2%)
HQ SNPs where both alleles are detected	42,415 (91.2%)	38,454 (82.6%)

Assessments are shown of the haploid and diploid coverage of the tumour and skin genomes from AML patient 933124. Chr, chromosome; hg18, human genome version 18; HQ, high quality.

Ley discloses additional computer processing of the data following an initial analysis using Maq. Specifically, “[b]ecause the number of sequence variants initially detected by Maq was high, we developed improved filtering tools to

effectively separate true variants from false positives. To this end, we generated an experimental data set by re-sequencing Maq-predicted SNVs, randomly selecting a training subset and a test data set, whose annotations and features were submitted to Decision Tree C4.5 (ref. 22).” One skilled in the art knew that Decision Tree C4.5 was a machine learning software tool implemented on a computer and even a casual reader of Ley would understand the nature of the Decision Tree C4.5 software tool based on the title of reference 22 to which Ley cites, “Quinlan, J. R. C4.5: Programs for Machine Learning 302 (Morgan Kaufmann Publishers, 1993).” Specifically, programs for machine learning are software tools implemented on computers to aid in the analysis of large data sets.

Ley discloses that “[w]e examined the Maq alignments by Decision Tree analysis to discover SNVs, as well as to identify copy number variants. Non-aligned reads were further analysed for indel discovery.” Ex. 1012 at 71. As Dr. Quackenbush explains, one skilled in the art knew, as discussed above, that Maq is a sequence alignment and analysis program designed to align sequence reads to a reference and in doing so identify positions at which the sequence contains genetic variants with respect to the reference. Ley discloses that a Decision Tree is a computational algorithm that is designed to filter and identify genetic variants appropriate for precision medicine applications. Quackenbush ¶¶112-13.

Ley compares the sequencing data from the tumor and normal sample to identify ten mutations in genes that occur in the tumor but not the normal sample (referred to as “acquired” or “somatic mutations”). “A total of ten non-synonymous somatic mutations were identified in this patient’s tumour genome.” Ex. 1012 at 70; Quackenbush ¶114.

c) “obtaining a probe set comprising a plurality of nucleic acid probe molecules ...”

Ley discloses obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid sequences or complements thereof and configured to selectively enrich or amplify sequences comprising variants over other sequences. Quackenbush ¶¶115-17. For example, *Ley* describes the design of PCR primers to bind to and selectively amplify the genetic variants identified in the biological sample:

By sequencing polymerase chain reaction (PCR)-generated amplicons from the tumour and skin samples (and also from the relapse tumour sample obtained 11 months after the original presentation), we determined that 152 of these variants were false positive (that is, wild type) calls, 14 were inherited SNPs, and eight were somatic mutations in both the original tumour and the relapse sample (Table 2).

Ex. 1012 at 69.

Ley further describes the design of PCR primers to bind to and selectively amplify sequences comprising the eight somatic mutations identified in the foregoing step: “To better define the percentage of tumour cells that contained each

of the discovered somatic mutations, we amplified each mutation-containing locus from non-amplified genomic DNA derived from the de novo and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and Table 3).” *Id.* at 69.

As Dr. Quackenbush explains, a POSA knew that sequencing PCR-generated amplicons required the design and use of nucleic acid probes designed to selectively enrich sequences comprising the set of genetic variants, such as the eight somatic variants previously described. Quackenbush ¶¶116-17. *Ley* teaches that these PCR probes are designed to selectively amplify such genetic variants (“each mutation-containing locus”) from the genome. *Id.* (“[W]e amplified each mutation-containing locus from non-amplified genomic DNA derived from the de novo and relapse tumour samples”). *Ley* further describes applying this same probe set to selectively amplify sequences in additional samples: “All of the PCR-amplified exons from the eight genes containing validated somatic mutations were sequenced in 187 further cases of AML using samples from our discovery and validation sets.” Ex. 1012 at 69. One skilled in the art knew that the coding portion of genes consist of smaller subunits known as exons and that *Ley* is describing amplifying and sequencing only

the small portion of each gene—the exon containing the genetic variant.

Quackenbush ¶117.

d) “using said probe set to selectively enrich or amplify sequences ...”

Ley discloses using the probe set of step (c) on an additional biological sample of the subject, *e.g.*, a sample from a “relapse tumor,” to generate a sequencing library. Quackenbush ¶118. For example, *Ley* uses the eight validated PCR probes corresponding to the genetic variants identified in the patient tumor plus two additional PCR probes set corresponding to exons in cancer-associated genes known to have common genetic variants, to selectively amplify sequences from both the original tumor and skin samples as well as one additional sample obtained from the patient’s relapsed disease, and to thereby generate amplicons comprising a sequencing library.: “[W]e amplified each mutation containing locus from non-amplified genomic DNA derived from the de novo and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and Table 3).” Ex. 1012 at 69; Quackenbush ¶118.

e) “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less ...”

Ley discloses subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a). Quackenbush ¶¶119-25.

For example, *Ley* discloses sequencing the sequencing library:

The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and Table 3). Control amplicons containing a known heterozygous SNP in BRCA2 (encoding N372H) and a homozygous SNP in TP53 (encoding P72R) were analysed similarly.

Ex. 1012 at 69.

As Dr. Quackenbush explains, the genes in Table 3 were the panel from which an exon containing a genetic variant was amplified from the original samples and from an additional relapse sample from the same individual, and that these resulting amplicons were subsequently sequenced. Quackenbush ¶120. A POSA knew that the assay was designed to target only the exons of the genes that contained the target genetic variants and that *Ley*'s panel of probes thus amplified only a small portion of the genome rather than the genome in its entirety. A POSA would also readily understand that the sequencing coverage of *Ley*'s panel of probes is "175 kb or less."

Id. As Dr. Quackenbush explains, even if all of the exons of every one of these genes were to be sequenced, the total combined sequence would only cover 45.254 kb, far less than the claimed upper limit of 175 kb. *Id.* at ¶121 (citing and summarizing NCBI records showing gene lengths).

Ley further teaches applying the panel of probes to the additional sample (relapse tumor sample) and then sequencing the resulting amplicons to “identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject” The sequencing results are summarized in Figure 3, which shows that each of the somatic mutations identified in the initial sample were also present in the relapse tumor sample:

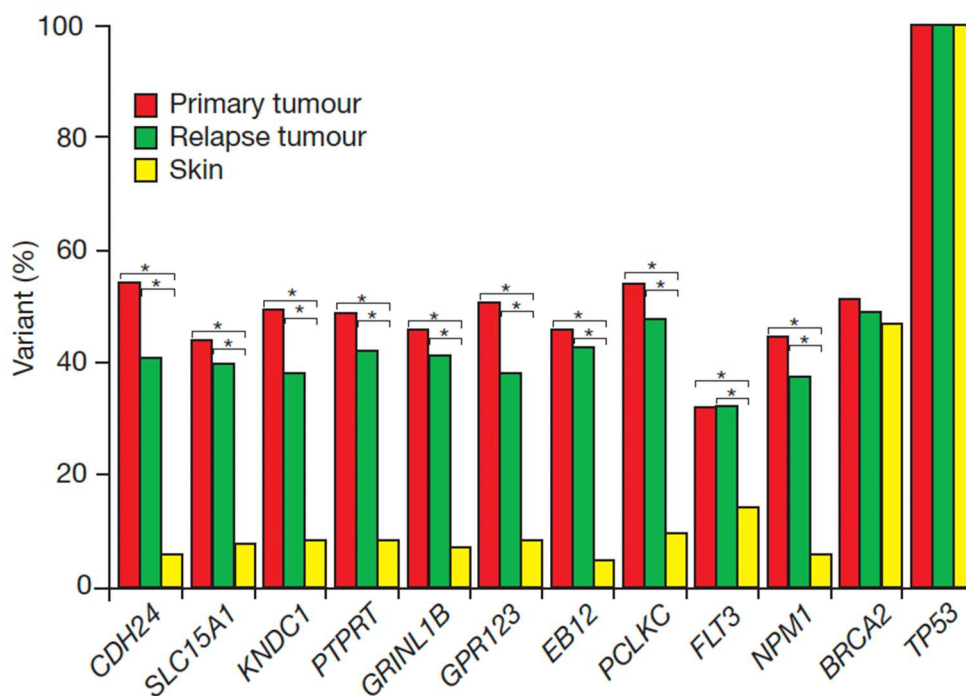


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that of the skin sample for all mutations ($P < 0.000001$ for all mutations, Fisher's exact test, denoted by a single asterisk in all cases). Note that the normal skin sample was contaminated with leukaemic cells containing the somatic mutations. The patient's white blood cell count was 105,000 (85% blasts) when the skin punch biopsy was obtained.

As Dr. Quackenbush explains, *Lev* further teaches that the sequencing depth of this step (e) (the targeted sequencing of the amplicons generated from the relapse tumor sample) ranged from 588-fold to 12,365-fold. That is far greater than the sequencing depth of the initial whole genome sequencing step of step (a), which was a depth of 32.7-fold for the tumor genome and 13.9-fold for the skin genome. Quackenbush at ¶123-25.

2. Claim 2

Claim 2 recites “[t]he method of claim 1, further comprising outputting a report that is generated at least based on comparison of results from said sequencing of (a) with results from at least said subjecting said sequencing library to said sequencing of (e).”

Ley anticipates claim 2. For example, *Ley* discloses a workflow involving whole-genome sequencing with the Illumina Genome Analyzer and Solexa sequencing platform to identify variants of interest. Quackenbush ¶¶126-30. Specifically, *Ley* describes “the use of whole-genome re-sequencing and variant discovery approaches using the Illumina/Solexa technology . . . to sequence a tumor genome of a single AML patient and the matched normal genome (derived from a skin biopsy) of the same patient.” Ex. 1012 at 67.

Ley further discloses generating a report, including by disclosing a tabular summary of results. For example, Table 1 is a table summarizing various results of sequencing 2 including reported information at least based on comparison of results from said sequencing of (a) with results from at least said subjecting said sequencing library to said sequencing of (e). *Id.* at 68; Quackenbush ¶129.

Table 1 | Tumour and skin genome coverage from patient 933124

	Tumour	Skin
Libraries	4	3
Runs	98	34
Reads obtained	5,858,992,064	2,122,836,148
Reads passing quality filter	3,025,923,365	1,228,177,690
Bases passing quality filter	98,184,511,523	41,783,794,834
Reads aligned by Maq	2,729,957,053	1,080,576,680
Reads unaligned by Maq	295,966,312	138,276,594
SNVs detected with respect to hg18 (no Y)	3,811,115	2,918,446
SNVs (chr 1–22) detected with respect to hg18	3,681,968 (100.0%)	2,830,292 (100.0%)
SNVs also present in dbSNP	2,368,458 (64.3%)	2,161,695 (76.4%)
SNVs also present in Venter genome	1,499,010 (40.7%)	1,383,431 (48.9%)
SNVs also present in Watson genome	1,573,435 (42.7%)	1,456,822 (51.5%)
SNVs not in dbSNP/Venter/Watson	1,223,830 (33.2%)	591,131 (20.9%)
SNVs not in dbSNP/Venter/Watson/skin	925,200 (25.1%)	—
HQ SNPs	46,494 (100.0%)	46,572 (100.0%)
HQ SNPs where reference allele is detected	42,419 (91.2%)	38,454 (82.6%)
HQ SNPs where variant allele is detected	43,164 (92.9%)	39,220 (84.2%)
HQ SNPs where both alleles are detected	42,415 (91.2%)	38,454 (82.6%)

Assessments are shown of the haploid and diploid coverage of the tumour and skin genomes from AML patient 933124.
Chr, chromosome; hg18, human genome version 18; HQ, high quality.

Ley's Figure 3 also provides a report depicting sequence information regarding the relative abundance of particular somatic and germline mutations that were observed in samples taken at (i) primary onset, and (ii) relapse. Ex. 1012 (Ley) at 69 (Fig. 3) (reproduced below). These abundances are compared to the frequency of the same polymorphic alleles present in the skin sample, which represents a control. The report of Figure 3 is based on comparison of results from the initial whole genome sequencing of step (a), which identified the somatic mutations of Figure 3, with results from subjecting the sequencing library generated from the relapse tumor sample to the sequencing of step (e), which are depicted by the green bars:

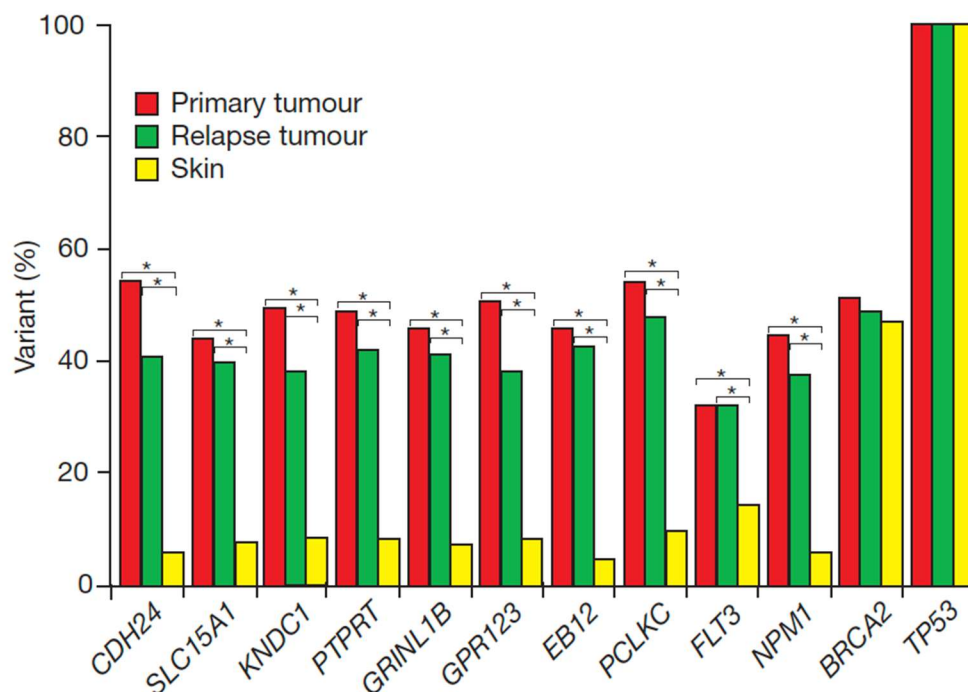


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that of the skin sample for all mutations ($P < 0.000001$ for all mutations, Fisher's exact test, denoted by a single asterisk in all cases). Note that the normal skin sample was contaminated with leukaemic cells containing the somatic mutations. The patient's white blood cell count was 105,000 (85% blasts) when the skin punch biopsy was obtained.

3. Claim 4

Claim 4 recites “[t]he method of claim 1, wherein said sequencing of (a) comprises (i) exome sequencing, (ii) sequencing a panel of genes, (iii) whole genome sequencing, and/or (iv) sequencing a population of complementary deoxyribonucleic acid molecules derived from ribonucleic acid molecules.”

Ley anticipates claim 4. Quackenbush ¶¶131-32. For example, *Ley's* “sequence data of (a)” is sequence information from whole genome sequencing. *Id.*

As Ley states, “[o]ur study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.” Ex. 1012 at 66; *see also supra* claim 1.

4. Claim 5

Claim 5 recites “[t]he method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).”

Ley anticipates claim 5. Quackenbush ¶¶133-36. For example, *Ley*’s personalized probe set comprises nucleic acid probe molecules—specifically PCR primers—that are directed to the genes described on the personalized tumor panel. *Id.* ¶134; Ex. 1012 at 71. Such PCR probes, by their nature, contain oligonucleotide-directed genomic content, specifically oligonucleotide sequences that base-pair or hybridize to their complementary sequences. Quackenbush ¶134.

Further, *Ley*’s PCR primers comprise “at least one variable portion from a result of said sequencing.” For example, *Ley* discloses including primers for the non-synonymous somatic mutations detected in the AML sample. Quackenbush ¶135. This part of *Ley*’s panel is “variable . . . from a result of said sequence data” at least because “eight [of ten] somatic mutations that [Ley] detected are all single base

changes, *and none has previously been detected in an AML genome.*” Ex. 1012 at 70; *see also id.* at 69 (“To better define the percentage of tumour cells that contained each of the discovered somatic mutations, we amplified each mutation-containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined.”); *id.* (Table 2); *id.* at 71 (“We cannot overemphasize the importance of parallel sequencing of the patient’s normal genome to determine which variants were inherited; the identification of the true somatic mutations in this tumour genome would not have been possible without this approach.”).

Ley’s PCR primers also comprise “at least one fixed portion independent of said result of said sequencing of (a).” For example, *Ley* discloses including primers for known mutations of the BRCA2 and TP53 genes. Ex. 1012 at 70 (Table 3, caption); *see also id.* at 69 (“Control amplicons containing a *known* heterozygous SNP in *BRCA2* (encoding N372H) and a homozygous SNP in *TP53* (encoding P72R) were analyzed similarly.”). The literature also confirmed that *BRCA2* and *TP53* were known AML tumor variants. *See* Ex. 1073 (Haferlach 2008) and Ex. 1074 (Misasa 1998) (confirming knowledge of such variants). The inclusion of these control amplicons were based on known genetic variants, which result in known

changes in the protein encoded, at a known gene dosage, and therefore constitute “fixed” probes independent of the variable probes that are selected and designed based on the identity of the patient-specific SNPs and other mutations identified via whole-genome sequencing of the patient’s tumor genome. Quackenbush ¶136; *see also supra* claim 1.

5. Claim 9

Claim 9 recites “[t]he method of claim 1, further comprising outputting a report that identifies said presence or absence of said at least said subset of said genetic variants in said subject or said at least one biological relative.”

Ley anticipates claim 9 for the same reasons discussed above with respect to claim 2. Quackenbush ¶¶137-38.

6. Claim 10

Claim 10 recites “[t]he method of claim 1, further comprising providing a therapeutic intervention at least based on said presence or absence of said at least said subset of said genetic variants identified in (e).”

Ley anticipates claim 10. Quackenbush ¶¶139-42. For example, in addition to the reasons given above with respect to claim 2, *Ley* discloses a report that informs a therapeutic intervention. *Id.* For example, *Ley* discloses that “[a]lthough the patient experienced a complete remission with conventional therapies, she relapsed at 11 months and expired 24 months after her initial diagnosis was made. At relapse the

bone marrow had 78% myeloblasts, and contained a new clonal cytogenetic abnormality.” Ex. 1012 at 67. Thus, *Ley’s* report, which shows elevated levels of certain variants, informs a therapy choice or a change (*e.g.*, switching away from conventional therapy, or resuming therapy upon relapse) for the subject. Quackenbush ¶140. For example, in the Supplementary Information, Ley presents the clinical and therapeutic implication of the SLC15A1. “LC15A1 is a transmembrane peptide transporter that is highly related to SLC11A1 (NRAMP1), SLC19A1, and SLC29A1 (ENT1), all of which are implicated in the transport of small molecules and drugs to cancer cells. Biallelic mutations in SCL29A1 that result in a lack of detectable protein recently have been associated with cytarabine resistance in a human leukemia cell line, implicating SLC family members in chemotherapy resistance for AML.” Ex. 1042. One skilled in the art would recognize that cytarabine is a chemotherapy drug use in the treatment of AML and that the presence of the SCL29A1 would inform an oncologist that the use of this drug was contraindicated.

Further, one skilled in the art would knew that the characteristics of the disease and the patient’s positive mutation in the FLT3 and NMP1 genes would contraindicate the use of allogenic stem cell transplant for this patient. “Based on available data, all adults with AML under age 60 years with matched siblings should be considered for allogeneic transplantation in first remission, except for those with

favorable risk cytogenetics and possibly those whose disease has normal cytogenetics and is FLT3/ITD negative and NPM1 positive.” Ex. 1075 (Davies).

Moreover, as explained above in Section V.F, an important aspect of reporting the results of cancer-monitoring assays is providing actionable information to healthcare providers. Thus, a POSA knew how to generate “a result report that is focused on the abnormalities that can lead directly to the best available therapy, direct a patient to an ongoing clinical trial, or result in some other actionable response from the treating oncologist.” Ex. 1014 (Ross) at 537. Ley’s Figure 3 is an example of such a result report which shows the presence or absence of a health condition (e.g., cancer, as indicated by the presence of tumor-derived somatic mutations) at different time points (e.g., upon presentation and at relapse) over the course of the patient’s cancer.

7. Claim 11

Claim 11 recites “[t]he method of claim 1, wherein said at least one biological sample includes a tumor sample and said nucleic acids molecules are from cells in said tumor sample.”

Ley anticipates claim 11. Quackenbush ¶¶143-44. For example, *Ley*’s initial whole-genome sequencing data is derived from sequences of nucleic acids taken from a primary tumor sample, *i.e.*, a tumor biopsy. *Id.*; *see also supra* claim 1.

8. Claim 13

Claim 13 recites “[t]he method of claim 1, wherein said plurality of nucleic acid sequences having said set of genetic variants comprises genetic variants in a germline sequence of said subject.”

Ley anticipates claim 13. Quackenbush ¶¶145-46. For example, **Ley** discloses that “[w]e sequenced the genome of normal skin cells from the same patient to enable the identification of inherited sequence variants in the tumor genome.” Ex. 1012 at 67. Normal skin cells have germline sequence as recited in the claim. For example, as shown in Ley’s Figure 3, the subject’s germline sequence had genetic variants in the BRCA2 and TP53 genes. *Id.* at 69; Quackenbush ¶146.

9. Claim 18

Claim 18 recites “[t]he method of claim 1, wherein subjecting said sequencing library to sequencing in (e) comprises generating nucleic acid sequence data from said additional biological sample.”

Ley anticipates claim 18. Quackenbush ¶¶147-48. For example, **Ley’s** sequencing library was created by amplifying the relapsed tumor sample with the set of PCR primers and the resulting amplicons were then sequenced. *Id.*; *see also supra* claim 1.

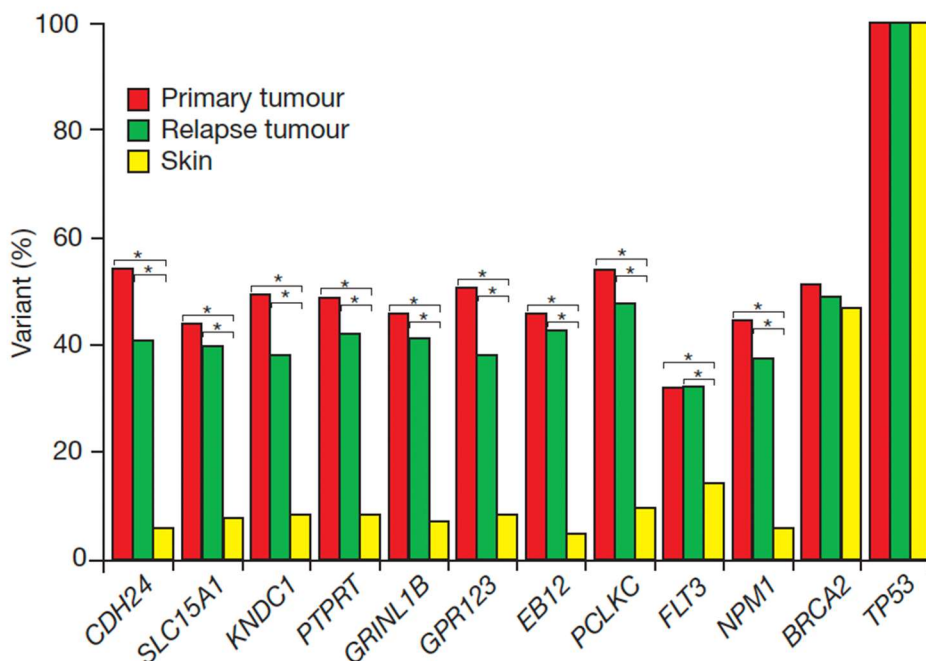


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that of the skin sample for all mutations ($P < 0.000001$ for all mutations, Fisher's exact test, denoted by a single asterisk in all cases). Note that the normal skin sample was contaminated with leukaemic cells containing the somatic mutations. The patient's white blood cell count was 105,000 (85% blasts) when the skin punch biopsy was obtained.

10. Claim 19

Claim 19 recites “[t]he method of claim 1, wherein computer processing of said sequence data comprises identifying one or more of (i) genetic variants of said nucleic acid sequence with respect to a germline sequence(s), (ii) alleles which match said reference sequence(s) and are correlated with a type of cancer or other disease, (iii) alleles which determine a human leukocyte antigen (HLA) type, (iv)

metrics of gene expression or allele-specific expression, and (v) quantification of non-coding ribonucleic acid (RNA) molecules or micro-RNA molecules which are at least partially tissue-type specific or cancer-type specific.”

Ley anticipates claim 19. Quackenbush ¶¶149-50. For example, the BRCA2 and TP53 genes included in *Ley*’s fixed panel are alleles which match said reference sequence(s) and are correlated with a type of cancer or other disease. *Id.* Further, as discussed above, *Ley*’s computer processing-based comparison of the whole genome sequence data from the primary tumor to the patient’s germline sequence identified a number of somatic mutations (acquired “genetic variants” found in the primary tumor) “with respect to a germline sequence.” *See* Ex. 1012 at 69, Figure 3.

11. Claim 28

Claim 28 recites “[t]he method of claim 1, further comprising using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.”

Ley anticipates claim 28 for the reasons given above with respect to claim 10. Quackenbush ¶¶151-56. *Ley*’s report also discloses genetic variants which inform treating a subject. Specifically, “[a]lthough the patient experienced a complete remission with conventional therapies, she relapsed at 11 months and expired 24 months after her initial diagnosis was made. At relapse, the bone marrow had 78%

myeloblasts, and contained a new clonal cytogenetic abnormality, t(10;12)(p12;p13).” Ex. 1012 at 67. Thus, *Ley’s* report (*e.g.*, Figure 3), which shows elevated levels of certain variants, informs a therapy choice or a change (*e.g.*, switching away from conventional therapy, or resuming therapy upon relapse) for the subject.

Ley’s Supplementary Information, Ex. 1042, provides a detailed case report and provides detailed information about a number of the various mutations that had been detected in the patient’s cancer genome. The germline and somatic genetic variants detected in the patient are linked by *Ley* to the diagnosis of AML. “Germline copy number variants (CNVs) also may have contributed to AML susceptibility in this patient. Among the genes that lie within intervals constitutionally deleted in this individual are WWOX, a tumor suppressor somatically deleted or translocated in a variety of solid tumors.”

In the Supplementary Information, *Ley* also presents the clinical and therapeutic implication of the SLC15A1. “SLC15A1 is a transmembrane peptide transporter that is highly related to SLC11A1 (NRAMP1), SLC19A1, and SLC29A1 (ENT1), all of which are implicated in the transport of small molecules and drugs to cancer cells. Biallelic mutations in SCL29A1 that result in a lack of detectable protein recently have been associated with cytarabine resistance in a human leukemia cell line, implicating SLC family members in chemotherapy resistance for AML.” One skilled in the art would recognize that cytarabine is a chemotherapy

drug use in the treatment of AML and that the presence of the SCL29A1 would inform an oncologist that the use of this drug was contraindicated.

Further, one skilled in the art knew that the characteristics of the disease and the patient's positive mutational in the FLT3 and NPM1 would contraindicate the use of allogenic stem cell transplant for this patient. "Based on available data, all adults with AML under age 60 years with matched siblings should be considered for allogeneic transplantation in first remission, except for those with favorable risk cytogenetics and possibly those whose disease has normal cytogenetics and is FLT3/ITD negative and NPM1 positive." Ex. 1075 (Davies 2007).

12. Claim 29

Claim 29 recites "[t]he method of claim 1, wherein said reference comprises a human reference sequence."

Ley anticipates claim 29. Quackenbush ¶¶157-58. For example, *Ley* discloses that "[t]o begin evaluating the quantity and quality of the detected sequence variants in the tumour and skin genomes, we compared the overlap and uniqueness of this genome's variants with respect to the James D. Watson and J. Craig Venter genomes, and to dbSNP (v127; Fig. 1)." Ex. 1012 at 67.

13. Claim 30

Claim 30 recites "[t]he method of claim 1, wherein said reference is a human reference sequence."

Ley anticipates claim 30 for the same reasons given with respect to claim 29.

B. Ground 2: Ley Renders Obvious Claims 1-5, 9-11, 13, 18, 19, 28-30

As set forth below and discussed with respect to *Ley* in Ground 1, and as explained by Dr. Quackenbush in paragraphs 161-177 of his declaration, the challenged claims would have been obvious over *Ley*.

1. Claims 1-5, 9-11, 13, 18, 19, 28-30

The challenged claims are discussed in Ground 1. To the extent they are not anticipated, they would have been obvious over *Ley*. Quackenbush ¶¶163-68.

For example, to the extent *Ley's* disclosure not anticipate the limitation in step 1(e) concerning “sequencing at a coverage of 175 kilobases (kb) or less,” a POSA would have found it obvious to sequence at a coverage of 175 kilobases (kb) or less based on *Ley's* disclosure. *Id.* at ¶164. This is particularly true in light of the fact that the '611 Patent does not attach any significance to the claimed coverage of 175kb—instead teaching simply that it is far less than the about 35 million bases typically sequenced in exome sequencing. *Id.* ¶165; Ex. 1001 at 35:1-5. But 150 kilobases or 200 kilobases or any other number significantly less than 35 million bases are also far less than about 35 million bases. For that reason, even if a POSA would not have recognized express disclosure in *Ley* of coverage of 175kb or less, modifying *Ley's* disclosure to provide coverage (a capture panel) of 175kb or less would have been obvious. Quackenbush ¶166.

Further, as Dr. Quackenbush explains, a POSA would have known that achieving a higher sequence depth in step 1(e) was desirable for increasing accuracy of detecting and quantifying mutations in tumors, and, for a given number of sequencing counts, the use of fewer oligonucleotide probes to target smaller genomic regions would lead to higher sequencing depth. *Id.* at ¶167. In addition, even though sequencing had become less expensive over the years prior to the '611 patent, a person of ordinary skill knew reducing sequencing costs further was desirable, and that smaller sequencing panels in step 1(e) could reduce sequencing costs.

A POSA would have reasonably expected to be successful in reducing coverage to 175kb or less by choosing an informative subset of genes to assay. *Id.* at ¶168. Dr. Quackenbush explains that providing capture panels of smaller coverage was *easier* than greater coverage, because smaller coverage was achieved by having fewer oligonucleotide probes—a simplifying factor in capture panel design and production. *Id.* A smaller panel also simplified computational analysis because the resulting data would be limited to the few genes that were represented in a personalized panel (of the approximately 25,000 genes encoding in the genome). *Id.*

2. Claim 3—Further Information Regarding Obviousness

Claim 3 recites “[t]he method of claim 1, wherein in said sequencing of (a), said at least one biological sample is obtained from said subject at a first time point, and wherein said additional biological sample is obtained from said subject or said

at least one biological relative at a second time point subsequent to said first time point.”

Claim 3 is obvious over *Ley*. Quackenbush ¶¶169-70. Given that a benefit of the assay is the ability to observe the course of a patient’s cancer and response to treatment, a POSA would have found it obvious to repeat the assay at a second time point, resulting in the collection of a second biological sample following the initial sample for analysis and sequencing using the Ley’s personalized probe sets. *Id.* A POSA would have reasonably expected success in analyzing multiple samples, given that it would have involved merely applying the techniques already proven to be successful at multiple time points. Indeed, soon after, Leary (Ex. 1002) and McBride (Ex. 1015) demonstrated the use of a similar assay design, by using whole-genome sequencing to identify genetic structural variants (as opposed to SNVs as in Ley), and to subsequently use those identified markers as targets for serial monitoring of tumor DNA in the blood plasma of patients with solid tumors at multiple (e.g., 6) time points. *See also* Ex. 1031 (Meyerson) at 687 (Table 1) (listing Ley and subsequent whole cancer genome studies).

3. Claim 5—Further Information Regarding Obviousness

Claim 5 recites “[t]he method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a)

and (ii) at least one fixed portion independent of said result of said sequencing of (a).”

Claim 5 is obvious over *Ley*. Quackenbush ¶¶171-77. In addition to the PCR probes comprising the fixed portion already included in *Ley*’s panel, a POSA reading *Ley* in view of the knowledge in the field would have also found it obvious to include probes targeted to genetic variants involved in the pharmacogenomics of cancer drugs, *i.e.*, genetic variants that were known to have companion diagnostics, as well as to tumor-driver mutations that were known in the art.

For example, as explained in Section V.F (“Providing Actionable Information to Healthcare Providers”) above, many effective cancer therapies are targeted to particular genetic mutations that present in certain forms of cancer. Examples include the blockbuster drug Herceptin targeting HER2 positive breast cancer (*i.e.*, forms of breast cancer carrying mutations in the HER2 gene), which was first introduced in 1998. *See* Ex. 1014 (Ross 2011) at 527 (“During the ensuing 12 years, interest in these ‘drug-test’ combinations, also referred to as ‘companion diagnostics,’ has increased exponentially as more anticancer agents have been approved and more new drugs have entered clinical trials based on biomarker profiles. The selection of anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) and the use of anti-EGFR monoclonal antibody therapeutics in colorectal cancer (CRC) are now firmly based

on pretreatment sequence determinations for hot spots in the EGFR (NSCLC) and KRAS (CRC) genes.”).

Relatedly, the identity of therapy/cancer pairs would have been readily ascertainable by one skilled in the art by accessing the treatment guidelines for a particular cancer promulgated by the National Comprehensive Cancer Network (called the NCCN Guidelines) which are widely used by oncologists to reference and define standard of care treatments. Similar information would have also been available from the FDA-approved prescribing information available for relevant drugs. To design a probe for relevant mutations identified in this manner, a POSA would have been able to determine the relevant sequence information from any one of the publicly available cancer databases, such as COSMIC, *see* Section V.B (“Genetic Mutations”), and then designed nucleic acid probes based on the techniques already known in the art and applied in the methods expressly disclosed by Ley. Accordingly, a POSA would have reasonably expected success in the predictable use of known information (regarding the sequences) and known techniques (the creation of nucleic acid probes to target such sequences) to add “fixed” probes to the types of assays described in Ley in order to provide information relevant to the selection and response to mutation-specific therapy pairings.

Additionally, as discussed above, a POSA would have been familiar with known mutations common in certain forms of cancer, which are recorded in

databases based on population-level studies. Applying PCR-based or capture-based targeting approaches to such mutations using nucleic acid probe molecules was known and discussed by *Ley*: “[H]ypothesis-driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed or capture-based methods is inherently limited, and will miss key mutations.” Ex. 1012 at 70. A POSA would have been motivated to combine candidate gene-based probes (fixed portion) in a panel with patient specific mutations discussed above (variable portion) in order to assess the cancer for known mutations in well-characterized and studied candidate genes in addition to patient-specific mutations. For example, as noted above, in many instances such genes may drive the course of the cancer and may be key targets for therapy. Further, such a combination of fixed and variable probes would overcome the limitations identified by *Ley* of a purely hypothesis-driven (fixed probe-only) approach.

Ley’s observation that the use of such probes may be limited does not teach away from including them in a tumor-monitoring panel. In fact, based on the knowledge of cancer biology gained between *Ley*’s publication and the priority date, a POSA would have known that one reason a targeted approach may miss such mutations is because of tumor heterogeneity. Tumor heterogeneity refers to the fact that genetic variants present in a cancer are not always uniformly dispersed across a tumor spatially, and that certain key variants may not be present in the tumor at all

times during the cancer's progression. *See, e.g.,* Ex. 1071 (Burrell) at 338 (“Extensive genetic and phenotypic variations exist not only between tumours (intertumour heterogeneity) but also within individual tumours (intratumour heterogeneity; Fig. 1). In tumours, populations of subclones can intermingle or be spatially separated, and this subclonal architecture varies dynamically throughout the disease course.”). This explains why sequencing a tumor sample may miss some of the patient's tumor-associated mutations at any given point in time along the course of the disease. As a result, it would have been obvious to include probes for selectively enriching such hotspot mutations (*i.e.*, the claimed fixed probes) in the panel in order to detect in subsequent samples the mutations previously identified via the WGS assay, but also mutations that were known to be common in the patient's type of cancer. A POSA would have been motivated to monitor hotspot mutations for a particular cancer (*i.e.*, the fixed probes) even in cases where they may not have been identified at the time of initial presentation or at the time of an initial whole-genome sequencing assay, as such mutations may present later in the course of the patient's cancer.

A POSA would have been able to readily create probes for such mutations using already known techniques. Indeed, **Ley** already recognized that such probes were well-known in the art, and thus would have reasonably expected success in including such “fixed” probes in a cancer-monitoring panel. Further, such fixed

probes would selectively amplify sequences comprising genetic variants in exactly the same way as *Ley*'s variable probes selectively amplified sequences comprising patient-specific genetic variants.

4. Claim 28—Further Information Concerning Obviousness

Claim 28 recites “[t]he method of claim 1, further comprising using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.”

Claim 28 is obvious over *Ley*. Quackenbush ¶¶178-79. As explained above in Section V.F, an important aspect of reporting the results of cancer-monitoring assays is providing actionable information to healthcare providers. A POSA would have been motivated to generate “a result report that is focused on the abnormalities that can lead directly to the best available therapy, direct a patient to an ongoing clinical trial, or result in some other actionable response from the treating oncologist.” Ex. 1014 (Ross) at 537. *Ley*'s Figure 3 is an example of such a result report, which shows the presence or absence of a health condition at different time points over the course of the patient's cancer. It would have been obvious to report similar information at each time point for which a sample was collected and analyzed in *Ley*'s assays as well as in assays that were obvious variants of those disclosed in *Ley*. Moreover, it would have been obvious to identify genetic variants which inform a therapy choice

or change in therapy in such a report, in particular in instances in which the panel of genetic variants included probes designed to detect and quantify genes associated with a companion therapeutic, as discussed above

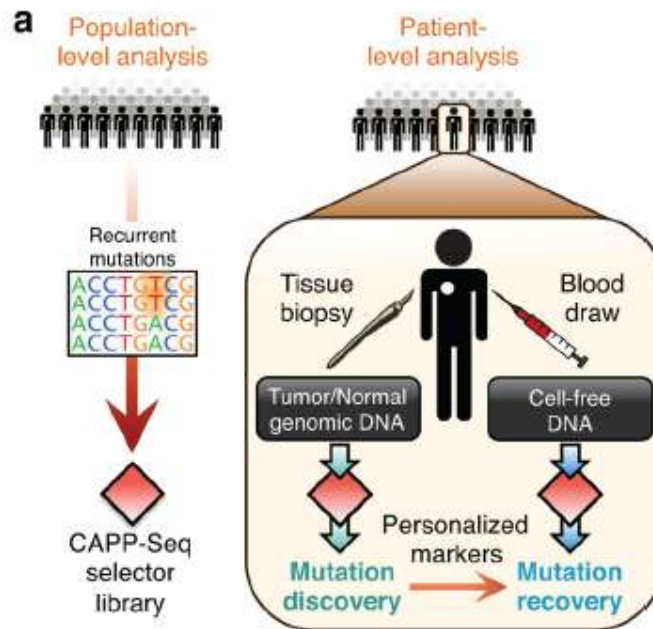
C. Ground 3: Newman Anticipates Claims 1-5, 9-11, 13, 18, 19, 28-30

As set forth below, and as explained by Dr. Quackenbush in paragraphs 180-227 of his declaration, the challenged claims are anticipated by *Newman*.

Newman describes a method for an improved “cancer personalized profiling by deep sequencing (CAPP-Seq)” which “combines hybrid affinity capture of hundreds of genomic regions with deep sequencing and a specialized bioinformatics workflow.” Ex. 1043 at 547. *Newman* reports that its method “substantially outperforms ... [other] methods for the analysis of ctDNA from clinically practical blood volumes and allows for efficient noninvasive ctDNA profiling in the absence of available tissue biopsies.” Ex. 1043 at 547.

The CAPP-Seq process “combines optimized library preparation methods for low DNA input masses with a multi-phase bioinformatics approach to design a “selector” consisting of biotinylated DNA oligonucleotides that target recurrently mutated regions in the cancer of interest. To monitor ctDNA, the selector is applied to tumor DNA to identify a patient’s cancer-specific genetic aberrations and then directly to circulating DNA to quantify them (Fig. 1a).” Ex. 1044 at 1

(“Introduction”); Quackenbush ¶181. Figure 1A from Newman 2014 is depicted below:



Newman applies this method to samples from a glioblastoma (GBM) tumor using a 157-kb personalized selector followed by targeted sequencing to cover mutations in the tumor that *Newman* discovered in its patient-level analysis of the tumor tissue. Quackenbush ¶182. Newman performed the patient-level analysis with whole exome sequencing of the glioblastoma tumor. Ex. 1043 at “ctDNA detection limits for iDES, duplex sequencing, and other methods” in “Online Methods.” That sequencing information was used to identify a number of somatic mutations, which in turn were targeted by the 157-kb personalized selector that used hybrid capture baits to selectively enrich the target sequences of the GBM tumor. *Id.* Newman “then applied this selector to perform deep resequencing of the GBM tumor (1/2 of a

MiSeq lane), and confirmed 97% of expected SNVs, 99.7% of which had duplex support (n = 1502).” *Id.*

1. Claim 1

Claim 1 recites “[a] method for personalized genetic testing” comprising method steps 1(a)-1(e). To the extent the preamble is limiting, *Newman* discloses it by stating, for example, that “[h]igh-throughput sequencing of circulating tumor DNA (ctDNA) promises to facilitated personalized cancer therapy.” Ex. 1043 at Abstract. *Newman*’s disclosure of the claimed method steps, as discussed further below, confirms that *Newman* meets the preamble. Quackenbush ¶¶185-86.

a) “sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more”

Newman discloses this step of the claimed method. Quackenbush ¶¶187-90. For example, as discussed above, *Newman* discloses CAPP-Seq. Exs. 1043, 1044.

Newman discloses that the sequencing comprises sequencing 12 gigabases (GB) or more. Quackenbush ¶188. As an initial matter, the ’611 patent does not ascribe any inventiveness to sequencing 12 gigabases or more. The ’611 patent discusses 12 gigabases only once in an example—Example 2—by stating that “a germline DNA sample can be exome sequenced (e.g., 12 billion bases).” Ex. 1001 at 62:33-35. The use of “e.g.” would have been understood by a person of ordinary skill to mean that 12 billion bases (gigabases) was simply an example of how much

exome sequencing could be used for the '611 patent method. As noted above, the range for whole exome sequencing was about 0.2 GB to 20 GB. Ex. 1040 at 123.

Newman discloses that “[s]equencing was performed using 2 x 100 or 2 x 150 paired-end reads” Ex. 1043 at “Library preparation and sequencing” in “Online Methods.” In its supplementary tables, published online together with and at the same time as *Newman*, *Newman* discloses data from whole exome sequencing—the same type of sequencing as in the '611 patent Example 2 discussing 12 GB of sequencing—of two samples from a glioblastoma patient. Ex. 1043 at Table 2, tab entitled “SuppTable2_samples_and_QC”, rows 286-87. In particular *Newman* reports that these two whole exome sequencing runs resulted in totals of 82,247,848 and 86,781,192 reads respectively. *Id.*

Sample number	Cohort	Case	Collection time ^a	Sample type	Input mass (ng)	Selector ^b	Sequencing adapter ^c	De-duplication ^d	Total reads
275	Healthy/Te	GBM-CTR25	GBM-CTR25-	cfDNA	32.0	GBM	Tandem	Barcoding	37,647,656
276	Healthy/Te	GBM-CTR26	GBM-CTR26-	cfDNA	32.0	GBM	Tandem	Barcoding	38,321,932
277	Healthy/Te	GBM-CTR27	GBM-CTR27-	cfDNA	32.0	GBM	Tandem	Barcoding	33,065,346
278	Healthy/Te	GBM-CTR28	GBM-CTR28-	cfDNA	32.0	GBM	Tandem	Barcoding	35,976,502
279	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	103,288,518
280	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	105,786,270
281	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	100,222,542
282	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	66,777,970
283	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	56,060,804
284	Technical	HD500-0.5%-i	HD500-0.5%-	Cell line bl	72.0	NSCLC tumor ge	Tandem	Barcoding	270,879,108
285	Healthy/Te	CTR31	CTR31-c1	cfDNA	32.0	NSCLC tumor ge	Tandem	Barcoding	259,725,374
286	GBM	GBM Relapse	na	Tumor	100.00	SeqCap EZ Hum.	Tandem	Barcoding	82,247,848
287	GBM	GBM PBL	na	PBL	100.00	SeqCap EZ Hum.	Tandem	Barcoding	86,781,192

Based on the 150 bp read length, the sequencing comprises sequencing 12.3 GB (150 * 82,247,848) and 13.0 GB (150 * 86,781,192) respectively. Accordingly, one species disclosed by *Newman* (i.e., the glioblastoma patient sequencing performed

using the 2 x 150 paired end read) anticipates the claim limitation of sequencing 12 gigabases or more. *See, e.g., Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346, (Fed. Cir. 1999) (“[A] single prior art species within the patent's claimed genus reads on the generic claim and anticipates.”).

b) “computer processing said sequencing ...”

Newman discloses this step of the claimed method. Quackenbush ¶¶191-93. For example, *Newman* performed whole exome sequencing on the glioblastoma tumor discussed above and found it to “harbor ~1,500 coding mutations.” Ex. 1043 at “ctDNA detection limits for iDES, duplex sequencing, and other methods” in “Online Methods.” These mutations are genetic variants in the tumor, and a person of ordinary skill would have understood *Newman* to be disclosing the use of computer processing to identify them because such large sequencing data sets were (and still are) always analyzed using computer processing in the field. *See* Ground 1, claim 1(b).

Further, the variants were identified with respect to a reference, *i.e.*, the unmutated sequences corresponding to the locations of the ~1,500 coding mutations. Quackenbush ¶192. As discussed above, *Newman’s* CAPP-Seq process, which was used for all the testing including for the glioblastoma tumor, includes producing a selector containing capture-based bait oligonucleotides corresponding to polymorphisms in a tumor. The selection of oligonucleotide probe sequences

requires comparison to a reference sequence (*i.e.*, the germline sequence for the GBM patient). *Id.*

c) “obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample”

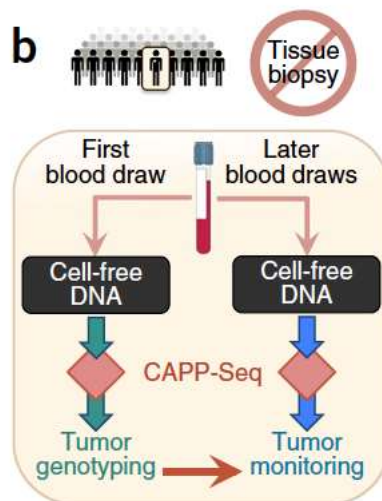
Newman discloses this step of the claimed method. Quackenbush ¶¶193-94. For example, *Newman* states that “[w]e designed a 157-kb ‘personalized’ selector to cover these [~1,500] mutations, employing the same biotinylated oligonucleotide synthesis process as described for the NSCLC selector design, above.” *Id.* For the referenced NSCLC selector design, *Newman* states that “[b]iotinylated oligonucleotide capture pools for both selectors were designed using the NimbleDesign portal (Roche NimbleGen) and genome build hg19 (NCBI Build 37.1/GRCh37).” *Id.* at “NSCLC selector design.”

Newman’s “[b]iotinylated oligonucleotide capture pools ... designed using the NimbleDesign portal (Roche NimbleGen)” are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample. For example, the NimbleGen system was known to be a commercially-available exome enrichment platform that used “biotinylated oligonucleotide baits complementary to exome targets” Ex. 1046 at 2. A person

of ordinary skill would have understood that such baits were used to enrich or amplify exome sequences over other sequences in a sample. It was also known that “exome sequencing [described in Clark] can be extended to general enrichment principles and custom enrichment assays. [Clark] demonstrated multiple levels of bait density and genome coverage that can be used as a guide when designing custom enrichment bait sets.” *Id.* at 9; *see also* Quackenbush ¶194.

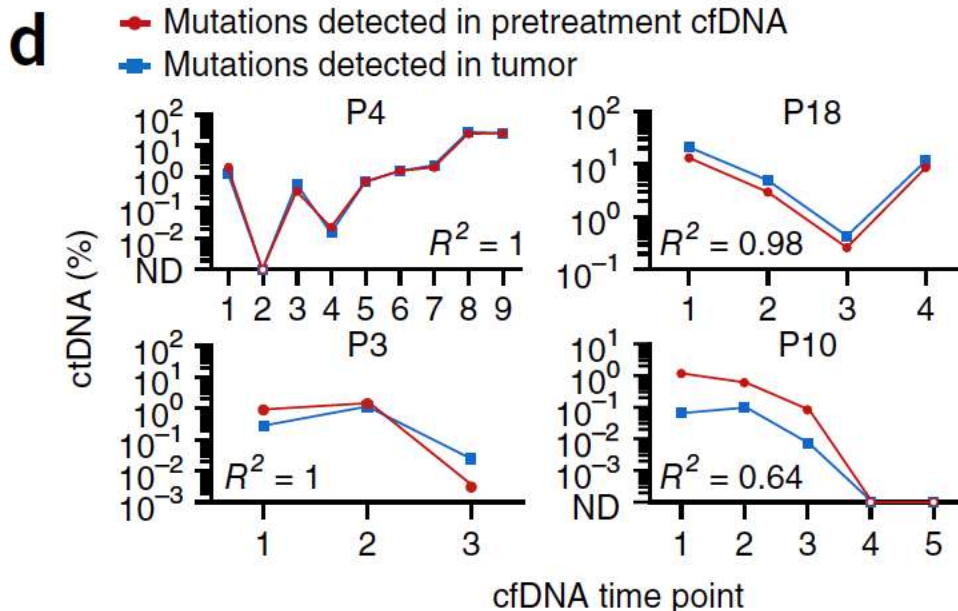
d) “using said probe set to selectively enrich or amplify sequences comprising said set of genetic ...”

Newman discloses this step of the claimed method. Quackenbush ¶¶195-96. For example, in Figure 1b, *Newman* discloses that “[l]ater blood draws” can be subjected to the same CAPP-Seq process as the “[f]irst blood draw.”



Newman also discloses in Figure 5d a time course study with multiple serial analyses on cfDNA or tumor DNA for a particular subject, which involve the use of the probe

set (*i.e.*, the 157 kb selector in the case of the GBM subject) for an additional biological sample from the subject.



Newman also disclosed creating a sequencing library. Quackenbush ¶¶196. For example, the “Seq” in CAPP-Seq stands for “deep sequencing” a sequencing library. *Id.* For the GBM subject, Newman “applied this selector [*i.e.*, the 157-kb selector for the ~1,500 coding mutations] to perform deep resequencing of the GBM tumor” *Id.* at “ctDNA detection limits for iDES, duplex sequencing, and other methods” in “Online Methods.”

e) “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less ...”

First, *Newman* discloses subjecting said sequencing library to sequencing at a coverage 157 kb, which is less than 175 kb. Quackenbush ¶¶186-88. Specifically, *Newman* discloses a 157 kb selector (capture panel) for the glioblastoma tumor,

which they used to generate a library for targeted sequencing to identify the presence or absence of genetic variants. *Id.* at “ctDNA detection limits for iDES, duplex sequencing, and other methods” in “Online Methods.” Second, *Newman’s* sequencing depth for this step (e) was greater than the sequencing depth of step (a) (the initial whole exome sequencing step). The supplementary table shows that the two glioblastoma samples were whole exome sequenced at median depths of 62 and 65 respectively. Ex. 1043 at Table 2, tab entitled “SuppTable2_samples_and_QC”, rows 286-87. In step (e), Newman “applied [his 157 kb] selector to perform deep resequencing of the GBM tumor (1/2 of a MiSeq lane)” *Id.* A POSA would have known that a MiSeq lane produced 4.5-5.1 Gb of sequencing data for 2 x 150 paired end reads. Quackenbush ¶198. Half of a lane would produce 2.25-2.55 Gb of sequencing data. The read depths are therefore calculated to be $(2.25 \times 10^9 \text{ bases} / 157,000 \text{ bases}) = 14,331$ to $(2.55 \times 10^9 \text{ bases} / 157,000 \text{ bases}) = 16,242$. Quackenbush ¶187.

In sum, Newman discloses sequencing depth 62 or 65 for (a), and sequencing depths of 14,331-16,242 for (e). Accordingly, the sequencing depth of (e) is greater than the sequencing depth of (a), as claimed. Quackenbush ¶199.

2. Claim 2

Claim 2 recites “[t]he method of claim 1, further comprising outputting a report that is generated at least based on comparison of results from said sequencing

of (a) with results from at least said subjecting said sequencing library to said sequencing of (e).”

Newman anticipates claim 2. Quackenbush ¶¶200-01. For example, at least in the described example of sequencing a tumor from a GBM patient, *Newman* performed whole exome sequencing and used the sequencing information to produce a 157-kb personalized selector (capture panel). *Id.* Newman “applied this selector to perform deep resequencing of the GBM tumor (1/2 of a MiSeq lane), and confirmed 97% of expected SNVs, 99.7% of which had duplex support (n = 1,502).” Ex. 1043 at “ctDNA detection limits for iDES, duplex sequencing, and other methods” in “Online Methods.” The outputs of 97% of expected SNVs and 99.7% having duplex support constitute reports generated based on comparison of the whole exome sequencing (the sequencing of (a)) to deep resequencing of the tumor (the sequencing of (e)). Quackenbush ¶201; *see also supra* claim 1.

3. Claim 3

Claim 3 recites “[t]he method of claim 1, wherein in said sequencing of (a), said at least one biological sample is obtained from said subject at a first time point, and wherein said additional biological sample is obtained from said subject or said at least one biological relative at a second time point subsequent to said first time point.”

Newman anticipates claim 3 for the same reasons discussed in connection with claim 1(d). Quackenbush ¶¶202-03; *id.* at ¶¶195-96.

4. Claim 4

Claim 4 recites “[t]he method of claim 1, wherein said sequencing of (a) comprises (i) exome sequencing, (ii) sequencing a panel of genes, (iii) whole genome sequencing, and/or (iv) sequencing a population of complementary deoxyribonucleic acid molecules derived from ribonucleic acid molecules.”

Newman anticipates claim 4 for the same reasons discussed in connection with claim 1(a), including that *Newman* performed whole exome sequencing for the glioblastoma tumor. Quackenbush ¶¶204-05; *id.* at ¶¶187-90.

5. Claim 5

Claim 5 recites “[t]he method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).”

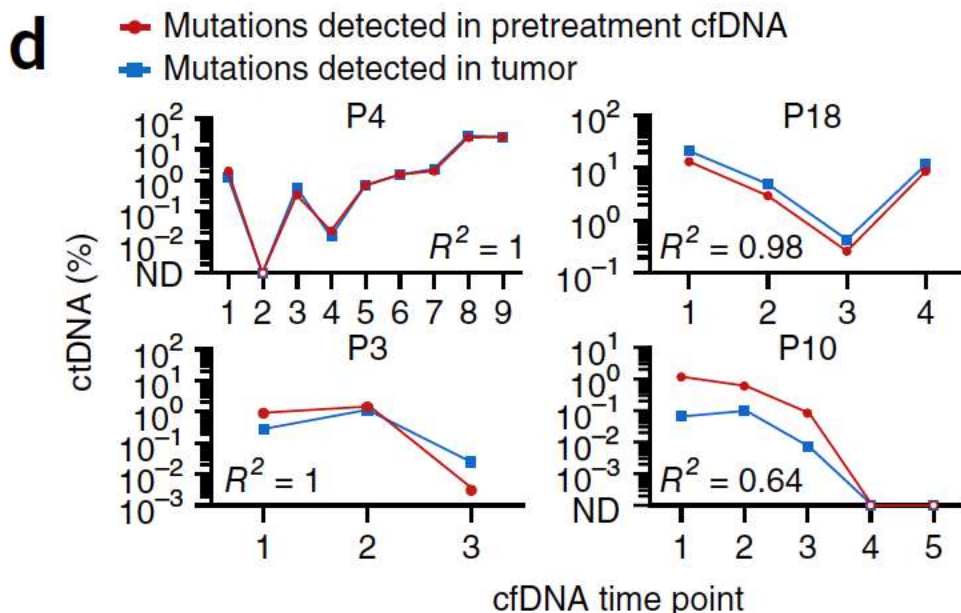
Newman anticipates claim 5. Quackenbush ¶¶206-08. For example, *Newman* discusses a plurality of nucleic acid probe molecules with at least one variable portion from a result of the sequencing of claim 1(a) for analysis of the glioblastoma tumor. The personalized selector used for the glioblastoma analysis contained

variable sequences based on the sequencing result of step 1(a). *Id.* at ¶205. Further, *Newman* taught designing a fixed selector “to target a median of at least eight mutations per NSCLC patient.” Ex. 1043 at “NSCLC selector design” in Online Methods.” All of the contents of these NSCLC selector panels are nucleic acid molecules with fixed sequences that are independent of the sequencing results of step 1(a). Quackenbush ¶208. Accordingly, *Newman* discloses a plurality of nucleic acid probe molecules with at least one fixed portion independent of the result of the step 1(a) sequencing. *Id.*

6. Claim 9

Claim 9 recites “[t]he method of claim 1, further comprising outputting a report that identifies said presence or absence of said at least said subset of said genetic variants in said subject or said at least one biological relative.”

Newman anticipates claim 9. Quackenbush ¶¶209-10. For example, Figure 5d in *Newman* is a report, in the form of a time course plot, identifying the presence (results above “ND,” or not detected) or absence (“ND”) of genetic variants (mutations) in the subject. *See also supra* claim 1.



7. Claim 10

Claim 10 recites “[t]he method of claim 1, further comprising providing a therapeutic intervention at least based on said presence or absence of said at least said subset of said genetic variants identified in (e).”

Newman anticipates claim 10. Quackenbush ¶¶211-12. For example, *Newman* discloses that “analysis of ctDNA is likely to play a major role in personalized cancer therapy by addressing several unmet clinical needs, including (i) noninvasive genotyping of clinically actionable tumor-derived variants *to guide therapy selection*, (ii) detection of emergent, actionable variants associated with *resistance during targeted therapy*, (iii) early measurement of *therapeutic responses*, and (iv) *detection of minimal residual disease* that is radiographically occult during disease surveillance.” Ex. 1043 at 554. *Newman’s* analysis of ctDNA

therefore discloses numerous types of therapeutic interventions based on the presence or absence of genetic variants, and the '611 patent makes clear that “[t]he therapeutic intervention may be a treatment or a report.” Ex. 1001 at 31:20-21. *See also* Quackenbush ¶212.

8. Claim 11

Claim 11 recites “[t]he method of claim 1, wherein said at least one biological sample includes a tumor sample and said nucleic acids molecules are from cells in said tumor sample.”

Newman anticipates claim 11. Quackenbush ¶¶213-15. For example, *Newman* discloses analysis of lung tumor samples, and specifically nucleic acid molecules from cells in lung tumor samples. Ex. 1043 at 548. Further, *Newman* “assessed iDES-enhanced CAPP-Seq genotyping using 66 serial plasma samples from patients with NSCLC, all of which had tumor biopsies available.” *Id.* at 551. *See also* Quackenbush ¶215.

9. Claim 13

Claim 13 recites “[t]he method of claim 1, wherein said plurality of nucleic acid sequences having said set of genetic variants comprises genetic variants in a germline sequence of said subject.”

Newman anticipates claim 13. Quackenbush ¶¶216-17. For example, in Supplementary Table 2, *Newman* reports a “Sample type” of “PBL” (which stands

for peripheral blood lymphocyte). Ex. 1045 at Table 2, tab entitled “SuppTable2_samples_and_QC”, rows 287. PBLs contain germline sequence, and *Newman’s* sequencing of PBLs resulted in a plurality of nucleic acid sequences having said set of genetic variants comprising genetic variants in a germline sequence of said subject. Quackenbush ¶217.

10. Claim 18

Claim 18 recites “[t]he method of claim 1, wherein subjecting said sequencing library to sequencing in (e) comprises generating nucleic acid sequence data from said additional biological sample.”

Newman anticipates claim 18. Quackenbush ¶¶218-19. For example, *Newman* discloses using an additional biological sample to generate a sequencing library, which is then used to generate sequence data in step 1(e). *See id.*; *id.* at ¶¶193-94. *See also supra* at claim 1.

11. Claim 19

Claim 19 recites “[t]he method of claim 1, wherein computer processing of said sequence data comprises identifying one or more of (i) genetic variants of said nucleic acid sequence with respect to a germline sequence(s), (ii) alleles which match said reference sequence(s) and are correlated with a type of cancer or other disease, (iii) alleles which determine a human leukocyte antigen (HLA) type, (iv) metrics of gene expression or allele-specific expression, and (v) quantification of

non-coding ribonucleic acid (RNA) molecules or micro-RNA molecules which are at least partially tissue-type specific or cancer-type specific.”

Newman anticipates claim 19. Quackenbush ¶¶220-21. For example, *Newman* discloses computer processing of the sequence data by identifying genetic variants of the nucleic acid sequence with respect to a germline sequence. *Id.* As Dr. Quackenbush explains, *Newman*’s study of a glioblastoma tumor to find ~1500 coding mutations involved comparison of the tumor sequences to germline sequences in peripheral blood lymphocytes (PBLs). *Id.* (citing Ex. 1043 at “ctDNA detection limits for iDES, duplex sequencing, and other methods” in “Online Methods”; Ex. 1045 at Sheet 2 (“Sample inventory with QC metrics”), rows 286-87). *See also supra* at claim 1.

12. Claim 28

Claim 28 recites “[t]he method of claim 1, further comprising using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.”

Newman anticipates claim 28. Quackenbush ¶¶222-23. For example, as discussed in connection with claim 10, *Newman* discloses using identified genetic variants to treat the subject. *Id.*; *see also supra* claims 1 and 10.

13. Claim 29

Claim 29 recites “[t]he method of claim 1, wherein said reference comprises a human reference sequence.”

Newman anticipates claim 29 at least because, for example, as discussed in connection with claim 19, *Newman* discloses the use of reference germline sequences from PBLs, which is a human reference sequence. Quackenbush ¶¶224-25.

14. Claim 30

Claim 30 recites “[t]he method of claim 1, wherein said reference is a human reference sequence.”

Newman anticipates claim 30 for the same reasons as discussed in connection with claim 29. Quackenbush ¶¶226-27.

D. Ground 4: Newman Renders Obvious Claims 1-5, 9-11, 13, 18, 19, 28-30

As set forth below and discussed with respect to *Newman* in Ground 3, and as explained by Dr. Quackenbush in paragraphs 228-243 of his declaration, the challenged claims would have been obvious over *Newman*.

1. Claims 1-5, 9-11, 13, 18, 19, 28-30

The challenged claims are discussed in Ground 3. To the extent they are not anticipated, they would have been obvious over *Newman*. Quackenbush ¶¶230-34.

For example, to the extent *Newman*’s disclosure does not anticipate the limitation in step 1(a) that the sequencing comprises 12 gigabases or more, a POSA

would have found it obvious to sequence 12 gigabases or more based on *Newman's* disclosure. *Id.* at ¶229. For example, *Newman* discloses that “[s]equencing was performed using 2 x 100 or 2 x 150 paired-end reads . . .” Ex. 1043 at “Library preparation and sequencing” in “Online Methods.” In its supplementary tables, published online together with and at the same time as *Newman*, Ex. 1060 (Newman Declaration)}, *Newman* discloses data from the sequencing of two samples from a glioblastoma patient. Ex. 1043 at Table 2, tab entitled “SuppTable2_samples_and_QC”, rows 286-87. *Newman* reports that these two sequencing runs resulted in totals of 82,247,848 and 86,781,192 reads respectively. *Id.*

Sample number	Cohort	Case	Collection time ^a	Sample type	Input mass (ng)	Selector ^b	Sequencing adapter ^c	De-duplication ^d	Total reads
275	Healthy/Te	GBM-CTR25	GBM-CTR25-	cfDNA	32.0	GBM	Tandem	Barcoding	37,647,656
276	Healthy/Te	GBM-CTR26	GBM-CTR26-	cfDNA	32.0	GBM	Tandem	Barcoding	38,321,932
277	Healthy/Te	GBM-CTR27	GBM-CTR27-	cfDNA	32.0	GBM	Tandem	Barcoding	33,065,346
278	Healthy/Te	GBM-CTR28	GBM-CTR28-	cfDNA	32.0	GBM	Tandem	Barcoding	35,976,502
279	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	103,288,518
280	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	105,786,270
281	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	100,222,542
282	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	66,777,970
283	Technical	GBM-Spike-0.	GBM-Spike-C	cfDNA	32.0	GBM	Tandem	Barcoding	56,060,804
284	Technical	HD500-0.5%-i	HD500-0.5%-	Cell line bl	72.0	NSCLC tumor ge	Tandem	Barcoding	270,879,108
285	Healthy/Te	CTR31	CTR31-c1	cfDNA	32.0	NSCLC tumor ge	Tandem	Barcoding	259,725,374
286	GBM	GBM Relapse	na	Tumor	100.00	SeqCap EZ Hum.	Tandem	Barcoding	82,247,848
287	GBM	GBM PBL	na	PBL	100.00	SeqCap EZ Hum.	Tandem	Barcoding	86,781,192

Using the 100 bp read length, the sequencing comprises 8.22 GB and 8.68 GB respectively.

A POSA would have been motivated to modify *Newman* such that the sequencing would be done with total reads that result in sequencing of 12GB or

more. As Dr. Quackenbush explains, the '611 patent does not ascribe any inventiveness to sequencing 12GB or more. Quackenbush ¶233. In fact, the '611 patent discusses 12GB only once when it states that “a germline DNA sample can be exome sequenced (e.g., 12 billion bases).” Ex. 1001 at 62:33-35. The use of “e.g.” would have been understood by a POSA to mean that 12 billion bases (gigabases) was simply an estimate of how much sequencing would probably be required for the '611 patent method, and a person of ordinary skill would have also understood and been motivated to modify *Newman* by the fact that more sequencing data would provide greater accuracy of the results. Quackenbush ¶233.

Further, there is nothing in *Newman* suggesting that sequencing of 12GB, for example, would not succeed. Quackenbush ¶234. As Dr. Quackenbush explains, Sims disclosed reports of whole exome sequencing in a broad range between about 0.2GB to 20GB. *Id.* At least because 12GB of sequencing is covered by the exome sequencing range in Sims, a POSA would have reasonably expected to achieve success by sequencing 12 GB or more for the glioblastoma samples rather than 8 GB. *Id.*

2. Claim 5—Further Information Regarding Obviousness

Claim 5 recites “[t]he method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a)

and (ii) at least one fixed portion independent of said result of said sequencing of (a).”

To the extent claim 5 is not anticipated, it would have been obvious over *Newman*. Quackenbush ¶¶235-243. *Newman* discloses a plurality of nucleic acid probe molecules with at least one fixed portion independent of the result of the step 1(a) sequencing. For example, in its “NSCLC selector design,” *Newman* taught designing a fixed selector “to target a median of at least eight mutations per NSCLC patient.” *Id.* at “NSCLC selector design” in Online Methods.” *Newman* also states that “additional clinically relevant regions were included ... to target actionable fusions in *ALK*, *ROS1*, and *RET* using intronic probes, and to ensure coverage of selected regions containing other actionable variants.” *Id.* All of the contents of these NSCLC selector panels are nucleic acid molecules with fixed sequences that are independent of the sequencing results of step 1(a).

There is no reason given in the ’611 patent why fixed sequences such as these could not be combined with variable sequences such as the ones used for the GBM patient’s tumor, and a person of ordinary skill in the art knew that a panel of 175 kb or less could be designed and produced with fixed and variable sequences.

In addition to the PCR probes comprising the fixed portion already included in *Newman*’s NSCLC selector, a POSA reading *Newman* in view of the knowledge in the field would have also found it obvious to include probes targeted to genetic

variants involved in the pharmacogenomics of cancer drugs, *i.e.*, genetic variants that were known to have companion diagnostics, as well as to tumor-driver mutations that were known in the art.

As Dr. Quackenbush explains, many effective cancer therapies are targeted to particular genetic mutations that present in certain forms of cancer. Examples include the blockbuster drug Herceptin targeting HER2 positive breast cancer (*i.e.*, forms of breast cancer carrying mutations in the HER2 gene), which was first introduced in 1998. *See* Ex. 1014 (Ross 2011) at 527 (“During the ensuing 12 years, interest in these ‘drug-test’ combinations, also referred to as ‘companion diagnostics,’ has increased exponentially as more anticancer agents have been approved and more new drugs have entered clinical trials based on biomarker profiles. The selection of anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) and the use of anti-EGFR monoclonal antibody therapeutics in colorectal cancer (CRC) are now firmly based on pretreatment sequence determinations for hot spots in the EGFR (NSCLC) and KRAS (CRC) genes.”).

Relatedly, the identity of therapy/cancer pairs would have been readily ascertainable by one skilled in the art by accessing the treatment guidelines for a particular cancer promulgated by the National Comprehensive Cancer Network (called the NCCN Guidelines) which are widely used by oncologists to reference

and define standard of care treatments. Similar information would have also been available from the FDA-approved prescribing information available for relevant drugs. To design a probe for relevant mutations identified in this manner, a POSA would have been able to determine the relevant sequence information from any one of the publicly available cancer databases, such as COSMIC, *see* Section V.B (“Genetic Mutations”), and then designed nucleic acid probes based on the techniques already known in the art and applied in the methods expressly disclosed by Ley. Accordingly, a POSA would have reasonably expected success in the predictable use of known information (regarding the sequences) and known techniques (the creation of nucleic acid probes to target such sequences) to add “fixed” probes to the types of assays described in Ley in order to provide information relevant to the selection and response to mutation-specific therapy pairings.

Additionally, as discussed above, a POSA would have been familiar with known mutations common in certain forms of cancer, which are recorded in databases based on population-level studies. A POSA would have been motivated to combine candidate gene-based probes (fixed portion) in a panel with patient specific mutations discussed above (variable portion) in order to assess the cancer for known mutations in well-characterized and studied candidate genes in addition to patient-specific mutations. For example, as noted above, in many instances such genes may drive the course of the cancer and may be key targets for therapy. Further, such a

combination of fixed and variable probes would overcome the limitations of a purely hypothesis-driven (fixed probe-only) approach, namely missing mutations in a particular patient sample.

A POSA would have known that one reason a targeted approach may miss such mutations is because of tumor heterogeneity. Tumor heterogeneity refers to the fact that genetic variants present in a cancer are not always uniformly dispersed across a tumor spatially, and that certain key variants may not be present in the tumor at all times during the cancer's progression. *See, e.g., Ex. 1071 (Burrell) at 338* ("Extensive genetic and phenotypic variations exist not only between tumours (intertumour heterogeneity) but also within individual tumours (intratumour heterogeneity; Fig. 1). In tumours, populations of subclones can intermingle or be spatially separated, and this subclonal architecture varies dynamically throughout the disease course."). This explains why sequencing a tumor sample may miss some of the patient's tumor-associated mutations at any given point in time along the course of the disease. As a result, it would have been obvious to include probes for selectively enriching such hotspot mutations (*i.e., the claimed fixed probes*) in the panel in order to detect in subsequent samples the mutations previously identified via the WGS assay, but also mutations that were known to be common in the patient's type of cancer. A POSA would have been motivated to monitor hotspot mutations for a particular cancer (*i.e., the fixed probes*) even in cases where they

may not have been identified at the time of initial presentation or at the time of an initial whole-genome sequencing assay, as such mutations may present later in the course of the patient's cancer.

A POSA would have been able to readily create probes for such mutations using already known techniques. Indeed, Newman already recognized that such probes were well-known in the art, and thus would have reasonably expected success in including such “fixed” probes in a cancer-monitoring panel. Further, such fixed probes would selectively enrich sequences comprising genetic variants in exactly the same way as variable probes selectively enrich sequences comprising patient-specific genetic variants.

XII. CONCLUSION

Petitioner respectfully submits that the Board should institute IPR and cancel the challenged claims.

Dated: February 10, 2023

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify, pursuant to 37 C.F.R. § 42.24, that the petition contains 13,852 words, excluding the words in the table of contents, exhibit list, claim listing, mandatory notices under § 42.8, this certificate of word count, and the certificate of service. The word count is based on the word count of the Microsoft Word program used to prepare the petition.

Dated: February 10, 2023

Respectfully submitted,

/ Andrew E. Krause /
Andrew E. Krause

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for *Inter Partes* Review of U.S. Patent No. 10,450,611 and Exhibits 1001-1003, 1005-1007, 1010, 1012-1015, 1019, 1023-1024, 1027-1029, 1031, 1037, 1040-1062, 1071, 1073-1075, and 1077 are being served via Express Mail on February 10, 2023, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent prosecution counsel of record for the Patent Owner:

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